

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
25 September 2008 (25.09.2008)

PCT

(10) International Publication Number
WO 2008/113760 A2

(51) International Patent Classification:

C07D 209/08 (2006.01) **C07D 401/12** (2006.01)
C07D 209/42 (2006.01) **C07C 311/21** (2006.01)
C07D 209/88 (2006.01) **A61K 31/404** (2006.01)
C07D 231/56 (2006.01) **A61K 31/4162** (2006.01)
C07D 235/08 (2006.01) **A61K 31/4184** (2006.01)
C07D 277/64 (2006.01) **A61K 31/381** (2006.01)
C07D 333/68 (2006.01) **A61K 31/423** (2006.01)
C07D 333/70 (2006.01)

173, 55216 Ingelheim Am Rhein (DE). **SCHOELCH, Corinna** [DE/DE]; Boehringer Ingelheim Gmbh, Cd Patents, Binger Str. 173, 55216 Ingelheim Am Rhein (DE). **SCHULER-METZ, Annette** [DE/DE]; Boehringer Ingelheim Gmbh, Cd Patents, Binger Str. 173, 55216 Ingelheim Am Rhein (DE). **PAUTSCH, Alexander** [DE/DE]; Boehringer Ingelheim Gmbh, Cd Patents, Binger Str. 173, 55216 Ingelheim Am Rhein (DE).

(21) International Application Number:

PCT/EP2008/053087

(22) International Filing Date: 14 March 2008 (14.03.2008)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

102007012284.7 16 March 2007 (16.03.2007) DE

(71) Applicant (for all designated States except US): **BOEHRINGER INGELHEIM INTERNATIONAL GMBH** [DE/DE]; Binger Str. 173, 55216 Ingelheim Am Rhein (DE).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **WAGNER, Holger** [DE/DE]; Boehringer Ingelheim Gmbh, Cd Patents, Binger Str. 173, 55216 Ingelheim Am Rhein (DE). **LANGKOPF, Elke** [DE/DE]; Boehringer Ingelheim Gmbh, Cd Patents, Binger Str. 173, 55216 Ingelheim Am Rhein (DE). **ECKHARDT, Matthias** [DE/DE]; Boehringer Ingelheim Gmbh, Cd Patents, Binger Str. 173, 55216 Ingelheim Am Rhein (DE). **STREICHER, Rüdiger** [DE/DE]; Boehringer Ingelheim Gmbh, Cd Patents, Binger Str.

(74) Agent: **HAMMANN ET AL., Heinz**; c/o BOEHRINGER INGELHEIM GMBH, Binger Str. 173, 55216 Ingelheim Am Rhein (DE).

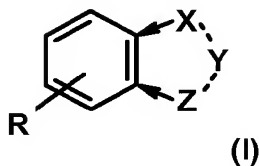
(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— without international search report and to be republished upon receipt of that report

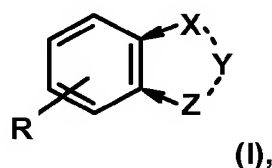
(54) Title: NEW SUBSTITUTED ARYLSULPHONYLGLYCINES, THE PREPARATION THEREOF AND THE USE THEREOF AS PHARMACEUTICAL COMPOSITIONS



(57) Abstract: The present invention relates to substituted arylsulphonyl glycines of general formula (I) wherein R, X, Y and Z are defined as in claim 1, the tautomers, enantiomers, diastereomers, mixtures thereof and salts thereof, which have valuable pharmacological properties, particularly the suppression of the interaction of glycogen phosphorylase a with the GL subunit of glycogen-associated protein phosphatase 1 (PP1), and their use as pharmaceutical compositions.

**New substituted arylsulphonylglycines, the preparation thereof
and the use thereof as pharmaceutical compositions**

The present invention relates to substituted arylsulphonylglycines of general formula I



wherein the groups R, X, Y and Z are defined as hereinafter, including the tautomers, stereoisomers, mixtures thereof and salts thereof. This invention further relates to pharmaceutical compositions containing a compound of formula I according to the invention as well as the use of a compound according to the invention for preparing a pharmaceutical composition for the treatment of metabolic disorders, particularly type 1 or type 2 diabetes mellitus. The invention also relates to processes for preparing a pharmaceutical composition as well as a compound according to the invention.

Compounds of formula I are suitable for preventing the inhibiting effect of glycogen phosphorylase on the activity of glycogen synthase by stopping the interaction of glycogen phosphorylase a with the G_L subunit of glycogen-associated protein phosphatase 1 (PP1). Compounds with these properties stimulate glycogen synthesis and are proposed for the treatment of metabolic disorders, particularly diabetes (P. Cohen, *Nature Reviews Molecular Cell Biology* **2006**, 7, 867-874).

5 **Aim of the invention**

The aim of the present invention is to provide new arylsulphonylglycines that suppress the interaction of glycogen phosphorylase a with the G_L subunit of glycogen-associated protein phosphatase 1 (PP1).

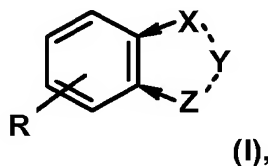
- 10 A further aim of the present invention is to provide new pharmaceutical compositions that are suitable for the prevention and/or treatment of metabolic disorders, particularly diabetes.

Another aim of this invention is to provide a process for preparing the
15 compounds according to the invention.

Other aims of the present invention will become directly apparent to the skilled man from the foregoing remarks and those that follow.

20 **Object of the invention**

In a first aspect the present invention relates to new substituted arylsulphonylglycines of general formula

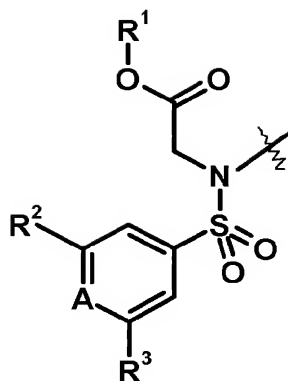


25

wherein

R denotes a group of formula

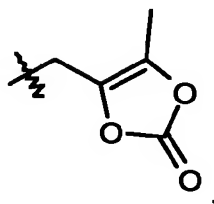
30



5

wherein

R^1 denotes H, C_{1-6} -alkyl or a group of formula



10

wherein the C_{1-6} -alkyl group mentioned for R^1 hereinbefore may be substituted by C_{1-6} -alkyl-carbonyloxy, C_{1-6} -alkoxy-carbonyloxy, C_{1-6} -alkoxy, hydroxy, amino, C_{1-3} -alkyl-amino, di-
 (C₁₋₃-alkyl)-amino, pyrrolidin-1-yl, piperidin-1-yl, morpholin-4-yl, piperazin-1-yl, 4-(C₁₋₃-alkyl)-piperazin-1-yl, aminocarbonyl, C₁₋₃-alkyl-aminocarbonyl, di-(C₁₋₃-alkyl)-aminocarbonyl, pyrrolidin-1-yl-carbonyl, piperidin-1-yl-carbonyl, morpholin-4-yl-carbonyl, piperazin-1-yl-carbonyl, 4-(C₁₋₃-alkyl)-piperazin-1-yl-carbonyl, tetrahydrofuran-3-yl-oxy, C₁₋₃-alkylamino-C₁₋₃-alkyloxy, di-(C₁₋₃-alkyl)-amino-C₁₋₃-alkyloxy, pyrrolidin-1-yl-C₁₋₃-alkyloxy, piperidin-1-yl-C₁₋₃-alkyloxy, morpholin-4-yl-C₁₋₃-alkyloxy, piperazin-1-yl-C₁₋₃-alkyloxy or 4-(C₁₋₃-alkyl)-piperazin-1-yl-C₁₋₃-alkyloxy,

15

20

25

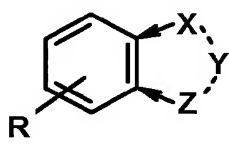
R^2 and R^3 independently of one another denote halogen, C_{1-3} -

5 alkyl, C₂₋₄-alkynyl, C₁₋₃-perfluoroalkyl, C₁₋₃-perfluoroalkoxy, C₁₋₃-alkoxy, cyano, nitro or hydroxy,

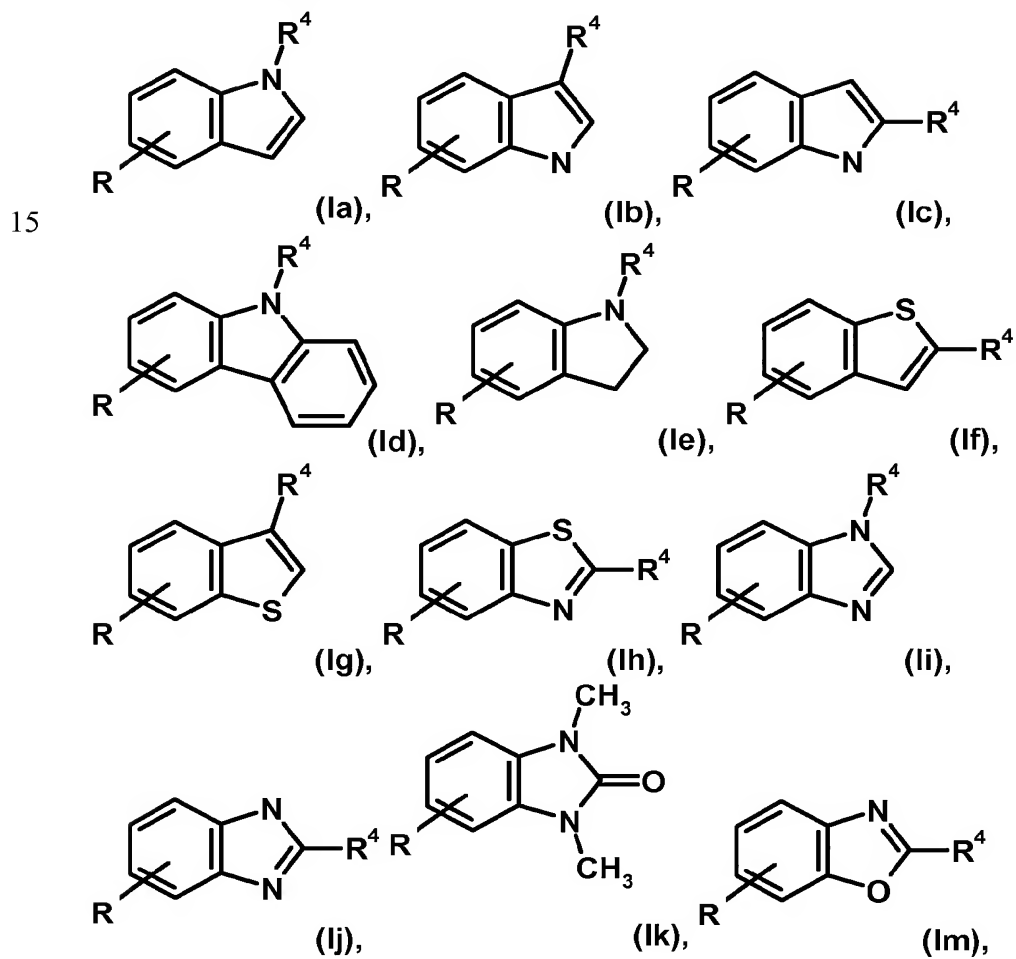
and

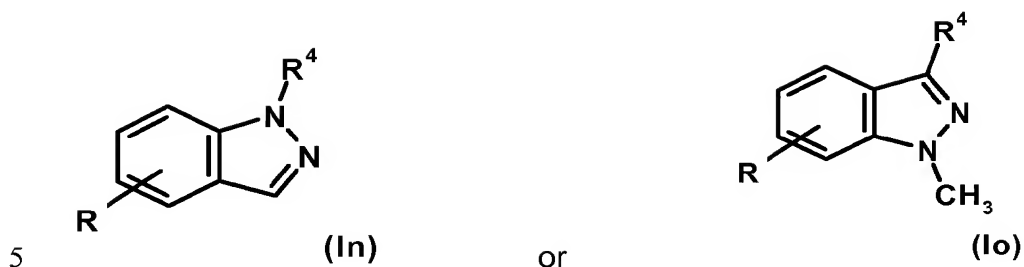
10 A denotes CH or N,

and the heterocyclic group



denotes a group of formula





wherein the above-mentioned heterocycles of formulae (Ia), (Ib), (Ic), (Ie), (If), (Ig), (Ii) and (In) may each optionally be substituted at the carbon atoms of the 5-ring by one or two groups selected from among

10 C₁₋₃-alkyl, amino-C₁₋₃-alkyl, hydroxy-C₁₋₃-alkyl, cyano, C₁₋₃-perfluoroalkyl, C₃₋₆-cycloalkyl, C₂₋₄-alkynyl, C₂₋₄-alkenyl, C₁₋₃-alkyl-carbonyl, C₁₋₃-perfluoroalkyl-carbonyl, carboxyl, C₁₋₃-alkyloxy-carbonyl, carboxy-C₁₋₃-alkyl, aminocarbonyl, C₁₋₃-alkyl-aminocarbonyl or di-(C₁₋₃-alkyl)-aminocarbonyl, wherein the groups may be identical or different

15 and each carbon atom may carry only one group, and

wherein the above-mentioned heterocyclic group of formula (Ib) may optionally be substituted at the nitrogen atom of the 5-ring by methyl or hydroxycarbonylmethyl, and wherein

20

R⁴ denotes H, cyano, C₁₋₆-alkyl, phenyl-C₁₋₆-alkyl, phenylsulphonyl-C₁₋₆-alkyl,

C₁₋₆-alkyl-carbonyl, carboxyl, C₁₋₆-alkoxy-carbonyl, phenylcarbonyl, phenyl-C₁₋₆-alkyl-carbonyl, 5-chloro-1H-indol-2-yl-carbonyl,

25

aminocarbonyl, C₁₋₆-alkyl-aminocarbonyl, di-(C₁₋₆-alkyl)-aminocarbonyl, C₃₋₆-cycloalkyl-aminocarbonyl, N-(C₃₋₆-cycloalkyl)-N-(C₁₋₆-alkyl)-aminocarbonyl, aryl-amino-carbonyl, N-oxy-pyridylamino-carbonyl,

30

4- to 7-membered cycloalkyleneimino-carbonyl optionally substituted by

- 5 hydroxy or C₁₋₃-alkyl-aminocarbonyl,
- morpholin-4-yl-carbonyl, piperazin-1-yl-carbonyl, 4-(C₁₋₃-alkyl)-
piperazin-1-yl-carbonyl, (piperazin-2-on-4-yl)-carbonyl,
- 10 aminocarbonyl-carbonyl, C₁₋₃-alkylaminocarbonyl-carbonyl, di-(C₁₋₃-
alkyl)-aminocarbonyl-carbonyl, pyrrolidin-1-ylcarbonyl-carbonyl,
piperidin-1-ylcarbonyl-carbonyl, morpholin-4-ylcarbonyl-carbonyl,
piperazin-1-ylcarbonyl-carbonyl, 4-methyl-piperazin-1-ylcarbonyl-
carbonyl,
- 15 C₁₋₃-alkyl-sulphonyl, phenyl-C₁₋₃-alkylsulphonyl or phenylsulphonyl
optionally substituted in the phenyl moiety by one or two chlorine
atoms,
- 20 wherein the C₁₋₆-alkyl-aminocarbonyl, di-(C₁₋₆-alkyl)-
aminocarbonyl and N-(C₃₋₆-cycloalkyl)-N-(C₁₋₆-alkyl)-amino-
carbonyl group mentioned above in the definition of R⁴ may each
be substituted in the alkyl moiety by aryl, C₁₋₃-alkyl-amino, di-(C₁₋₃-
alkyl)-amino, C₃₋₆-cycloalkyl-amino, N-(C₃₋₆-cycloalkyl)-N-(C₁₋₆-
25 alkyl)-amino, pyrrolidin-1-yl, piperidin-1-yl, morpholin-4-yl,
piperazin-1-yl, 4-methyl-piperazin-1-yl or C₁₋₃-
alkylaminocarbonyl, and
- wherein the aryl group mentioned above in the definition of R⁴ is
30 a 6-membered aromatic system that may contain 0 to 3 nitrogen
atoms and may be substituted by nitro.

The invention also relates to the tautomers, stereoisomers, mixtures and
salts, particularly the physiologically acceptable salts, of the compounds
35 according to the invention.

5 The compounds of general formula I according to the invention and the physiologically acceptable salts thereof have valuable pharmacological properties, in particular they suppress the interaction of glycogen phosphorylase a with the G_L-subunit of glycogen-associated protein phosphatase 1 (PP1).

10

Therefore this invention also relates to the use of the compounds according to the invention, including the physiologically acceptable salts, as pharmaceutical compositions.

15 The compounds of the above general formula I, wherein R¹ does not represent hydrogen, but denotes one of the other groups specified, are so-called prodrugs. By prodrugs are meant compounds that are not active *per se* but are converted into the corresponding active compound *in vivo*, cleaving the prodrug group.

20

This invention further relates to pharmaceutical compositions containing at least one compound according to the invention or a physiologically acceptable salt according to the invention, optionally together with one or more inert carriers and/or diluents.

25

A further object of this invention is the use of at least one compound according to the invention or a physiologically acceptable salt of such a compound for preparing a pharmaceutical composition that is suitable for the treatment or prevention of diseases or conditions that can be influenced by
30 suppressing the interaction of glycogen phosphorylase a with the G_L-subunit of glycogen-associated protein phosphatase 1 (PP1).

The invention also relates to the use of at least one compound according to the invention for preparing a pharmaceutical composition which is suitable for
35 the treatment of metabolic disorders, for example type I or II diabetes mellitus.

- 5 The invention also relates to the use of at least one compound according to the invention for preparing a pharmaceutical composition for suppressing the interaction of glycogen phosphorylase a with the G_L-subunit of glycogen-associated protein phosphatase 1 (PP1).
- 10 A further object of this invention is a process for preparing a pharmaceutical composition according to the invention, characterised in that a compound according to the invention is incorporated in one or more inert carriers and/or diluents by a non-chemical method.
- 15 The present invention also relates to a process for preparing the compounds of general formula I according to the invention.

Detailed description of the invention

- 20 Unless stated otherwise, the groups, radicals and substituents, particularly R, R¹ to R⁴, X, Y, Z and A have the meanings given hereinbefore and hereinafter.

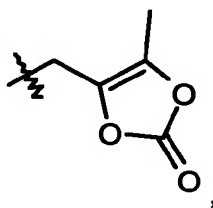
If groups, substituents or radicals occur more than once in a compound, they
25 may have the same or different meanings.

Preferred compounds of the above general formula I are those wherein

R denotes a group of the above-mentioned formula wherein

30

R¹ denotes H, C₁₋₆-alkyl or a group of formula



5

10

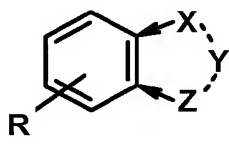
wherein the C₁₋₆-alkyl group mentioned for R¹ hereinbefore may be substituted by C₁₋₆-alkyl-carbonyloxy, C₁₋₆-alkoxy-carbonyloxy, C₁₋₆-alkoxy, hydroxy, amino, C₁₋₃-alkyl-amino, di-(C₁₋₃-alkyl)-amino, pyrrolidin-1-yl, piperidin-1-yl, morpholin-4-yl, piperazin-1-yl, 4-(C₁₋₃-alkyl)-piperazin-1-yl, aminocarbonyl, C₁₋₃-alkyl-aminocarbonyl, di-(C₁₋₃-alkyl)-aminocarbonyl, pyrrolidin-1-yl-carbonyl, piperidin-1-yl-carbonyl, morpholin-4-yl-carbonyl, piperazin-1-yl-carbonyl or 4-(C₁₋₃-alkyl)-piperazin-1-yl-carbonyl,

15

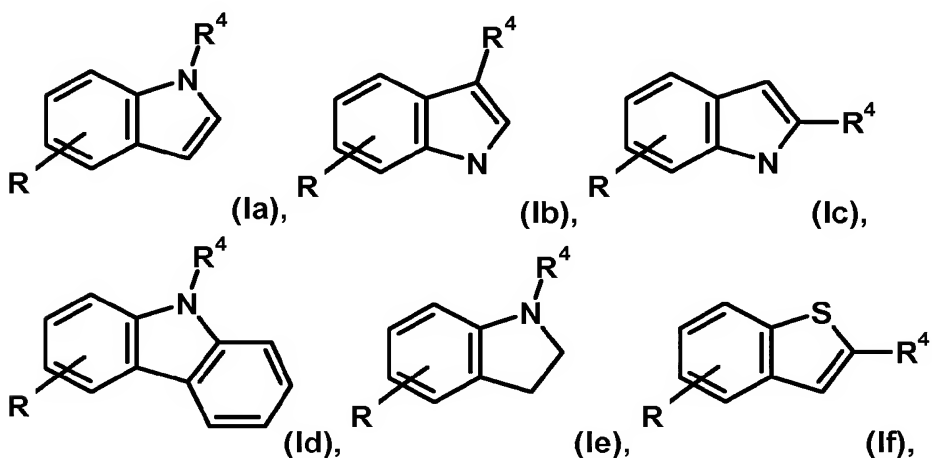
R² and R³ independently of one another denote halogen, C₁₋₃-alkyl, C₂₋₄-alkynyl, C₁₋₃-perfluoroalkyl, C₁₋₂-alkoxy or cyano and

A denotes CH or N,

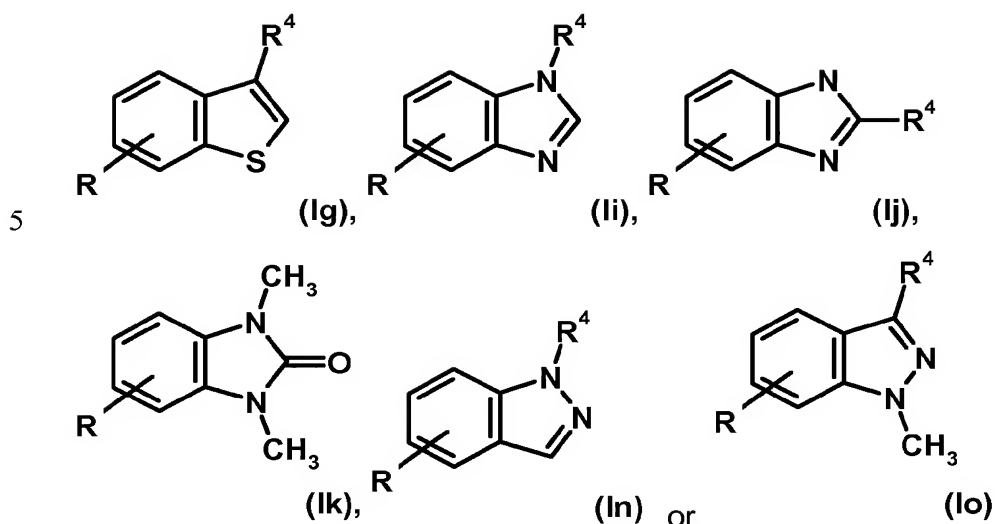
20 and the heterocyclic group



denotes a group of formula



25



10 wherein the above-mentioned heterocycles of formulae (Ia), (Ib), (Ic), (Ie), (If), (Ig), (Ii) and (In) may each optionally be substituted at the carbon atoms of the 5-ring by one or two groups selected from among C₁₋₃-alkyl, amino-C₁₋₃-alkyl, hydroxy-C₁₋₃-alkyl, cyano, C₃₋₆-cycloalkyl, C₁₋₃-alkyl-carbonyl, C₁₋₃-perfluoroalkyl-carbonyl, carboxyl, C₁₋₂-alkyloxy-carbonyl, carboxy-C₁₋₂-alkyl, aminocarbonyl, C₁₋₃-alkyl-aminocarbonyl or di-(C₁₋₃-alkyl)-aminocarbonyl, wherein the groups may be identical or

15 different and each carbon atom may carry only one group, and

20 wherein the above-mentioned heterocyclic group of formula (Ib) may optionally be substituted at the nitrogen atom of the 5-ring by methyl or hydroxycarbonylmethyl, and wherein

25 R⁴ denotes H, cyano, C₁₋₄-alkyl, phenyl-C₁₋₄-alkyl, phenylsulphonyl-C₁₋₄-alkyl,

C₁₋₄-alkyl-carbonyl, carboxyl, C₁₋₄-alkoxy-carbonyl, phenylcarbonyl, phenyl-C₁₋₄-alkyl-carbonyl, 5-chloro-1H-indol-2-yl-carbonyl,

aminocarbonyl, C₁₋₄-alkyl-aminocarbonyl, di-(C₁₋₄-alkyl)-aminocarbonyl,

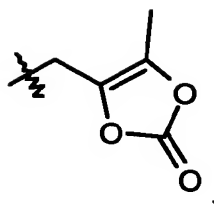
- 5 C₃₋₆-cycloalkyl-aminocarbonyl, N-(C₃₋₆-cycloalkyl)-N-(C₁₋₄-alkyl)-amino-carbonyl, [N,N-di-(C₁₋₄-alkyl)-amino]-C₁₋₃-alkyl-amino-carbonyl, 1-(methylaminocarbonyl)-ethyl-amino-carbonyl, aryl-amino-carbonyl, aryl-C₁₋₃-alkyl-amino-carbonyl, N-oxy-pyridylamino-carbonyl,
- 10 4- to 7-membered cycloalkyleneimino-carbonyl optionally substituted by hydroxy or methylaminocarbonyl,
- morpholin-4-yl-carbonyl, piperazin-1-yl-carbonyl, 4-(methyl)-piperazin-1-yl-carbonyl, (piperazin-2-on-4-yl)-carbonyl,
- 15 aminocarbonyl-carbonyl, C₁₋₂-alkylaminocarbonyl-carbonyl, di-(C₁₋₂-alkyl)-aminocarbonyl-carbonyl, pyrrolidin-1-ylcarbonyl-carbonyl, piperidin-1-ylcarbonyl-carbonyl, morpholin-4-ylcarbonyl-carbonyl,
- 20 C₁₋₂-alkyl-sulphonyl, phenyl-C₁₋₂-alkyl-sulphonyl or phenylsulphonyl optionally substituted in the phenyl moiety by one or two chlorine atoms,
- 25 while the aryl group mentioned above in the definition of R⁴ is a 6-membered aromatic system that may contain 0 to 2 nitrogen atoms and may be substituted by nitro.

Particularly preferred are those compounds of the above general formula I,
30 wherein

R denotes a group of the above-mentioned formula wherein

R¹ denotes H, C₁₋₄-alkyl or a group of formula

5



10

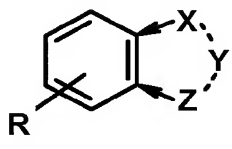
wherein the C₁₋₄-alkyl group mentioned for R¹ hereinbefore may be substituted by C₁₋₄-alkoxy, hydroxy, di-(C₁₋₃-alkyl)-amino, pyrrolidin-1-yl, piperidin-1-yl, morpholin-4-yl, piperazin-1-yl or 4-(methyl)-piperazin-1-yl,

R² and R³ independently of one another denote chlorine, bromine, C₁₋₂-alkoxy, C₂₋₃-alkynyl or C₁₋₂-alkyl and

15

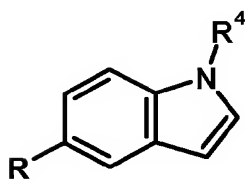
A denotes CH or N,

and the heterocyclic group

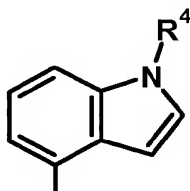


denotes a group of formula

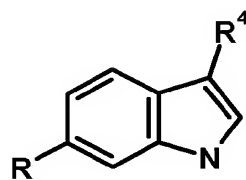
20



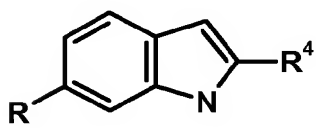
(Ia1),



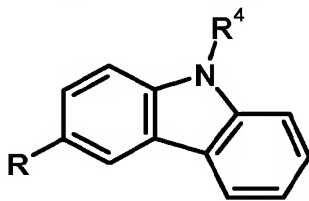
(Ia2),



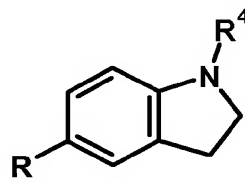
(Ib1),



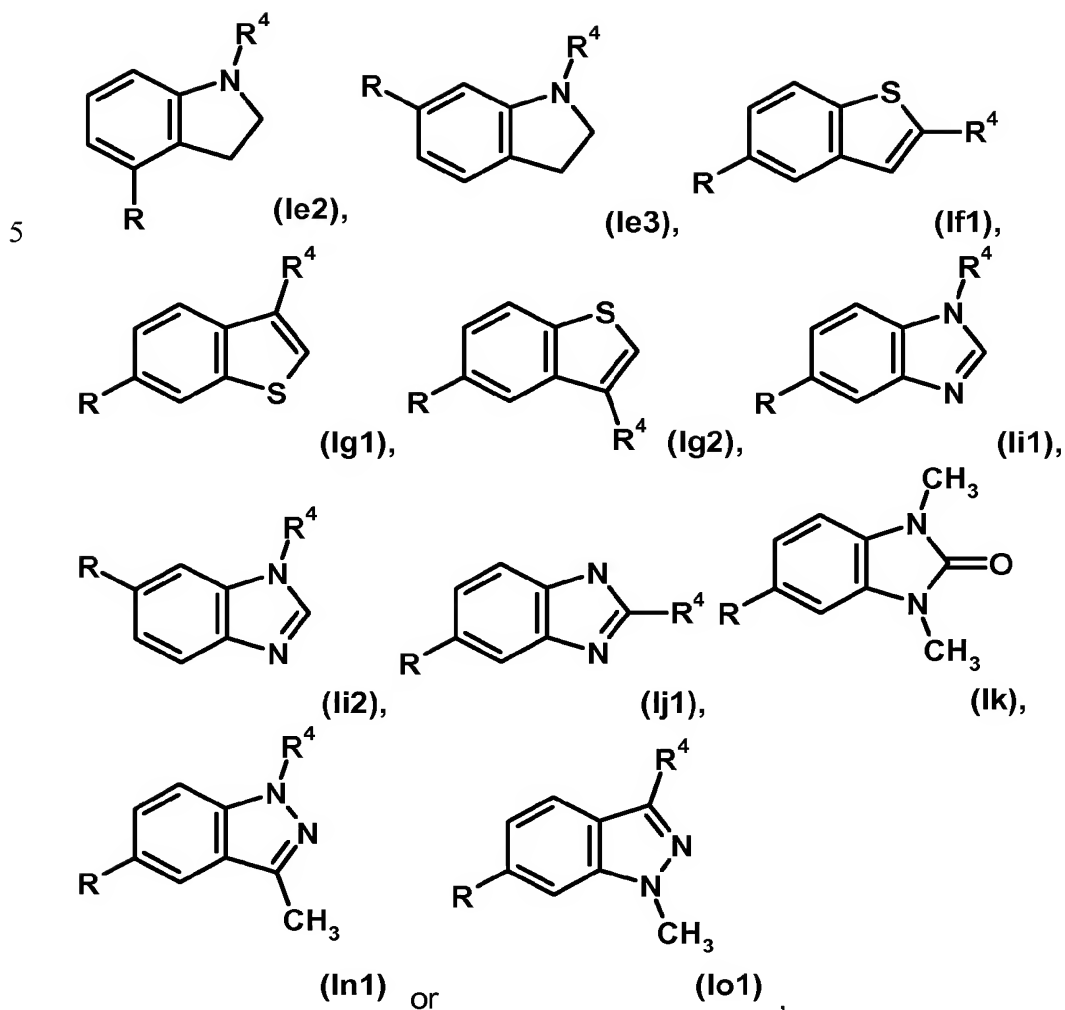
(Ic1),



(Id1),



(Ie1),



10 wherein the above-mentioned heterocycles of formulae (la1), (la2) and (le1) may each optionally be substituted at the carbon atoms of the 5 ring by a group selected from among C₁₋₂-alkyl, methylcarbonyl, trifluoromethylcarbonyl, carboxyl, methoxy-carbonyl, aminocarbonyl, methyl-aminocarbonyl, dimethyl-aminocarbonyl, aminomethyl or

15 hydroxymethyl, and

wherein the above-mentioned heterocyclic group of formula (lb1) may optionally be substituted at the nitrogen atom of the 5 ring by methyl or hydroxycarbonylmethyl, and wherein

20

5 R^4 denotes H, cyano, C_{1-4} -alkyl, phenyl- C_{1-4} -alkyl, phenylsulphonyl- C_{1-4} -alkyl,

C_{1-4} -alkyl-carbonyl, carboxyl, C_{1-4} -alkoxy-carbonyl, phenylcarbonyl, phenyl- C_{1-4} -alkyl-carbonyl, 5-chloro-1H-indol-2-yl-carbonyl,

10

aminocarbonyl, C_{1-4} -alkyl-aminocarbonyl, di-(C_{1-4} -alkyl)-aminocarbonyl, C_{3-6} -cycloalkyl-aminocarbonyl, N-(C_{3-6} -cycloalkyl)-N-(C_{1-4} -alkyl)-aminocarbonyl, N,N-di-(C_{1-3} -alkyl)-amino- C_{1-3} -alkyl-amino-carbonyl, 1-(methylaminocarbonyl)-ethyl-amino-carbonyl, phenylamino-carbonyl, 15 (nitrophenyl)-amino-carbonyl, phenyl- C_{1-2} -alkyl-amino-carbonyl, pyridinylamino-carbonyl, pyrazinylamino-carbonyl, N-oxy-pyridylamino-carbonyl,

20

azetidin-1-yl-carbonyl, pyrrolidin-1-yl-carbonyl, 3-hydroxy-pyrrolidin-1-yl-carbonyl, 2-(methylaminocarbonyl)-pyrrolidin-1-yl-carbonyl, piperidin-1-yl-carbonyl, morpholin-4-yl-carbonyl, piperazin-1-yl-carbonyl, (piperazin-2-on-4-yl)-carbonyl,

25

aminocarbonyl-carbonyl, C_{1-2} -alkylaminocarbonyl-carbonyl, di-(C_{1-2} -alkyl)-aminocarbonyl-carbonyl, pyrrolidin-1-ylcarbonyl-carbonyl, piperidin-1-ylcarbonyl-carbonyl, morpholin-4-ylcarbonyl-carbonyl,

benzyl-sulphonyl, phenylsulphonyl or 3,5-dichloro-phenyl-sulphonyl,

30

but particularly those compounds of the above general formula I, wherein

R denotes a group of the above-mentioned formula wherein

35 R^1 denotes H or a C_{1-3} -alkyl group optionally substituted by a di-(C_{1-3} -alkyl)-amino group,

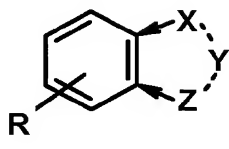
5

R^2 and R^3 independently of one another represent chlorine, ethynyl, methoxy, methyl or ethyl and

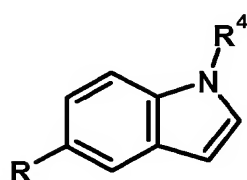
A denotes CH or N,

10

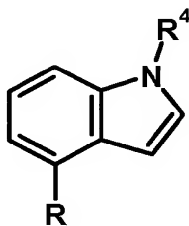
and the heterocyclic group



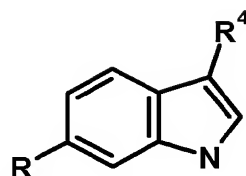
denotes a group of formula



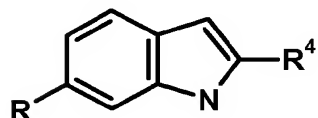
(Ia1),



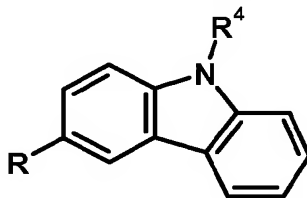
(Ia2),



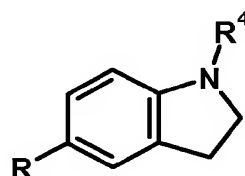
(Ib1),



(Ic1),

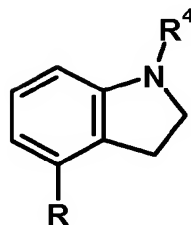


(Id1),

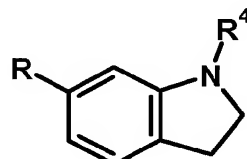


(Ie1),

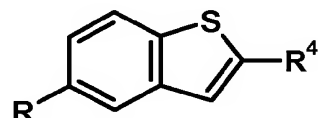
15



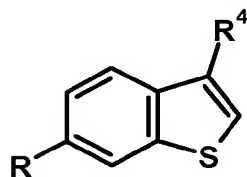
(Ie2),



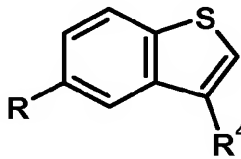
(Ie3),



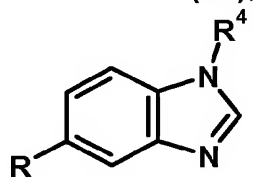
(If1),



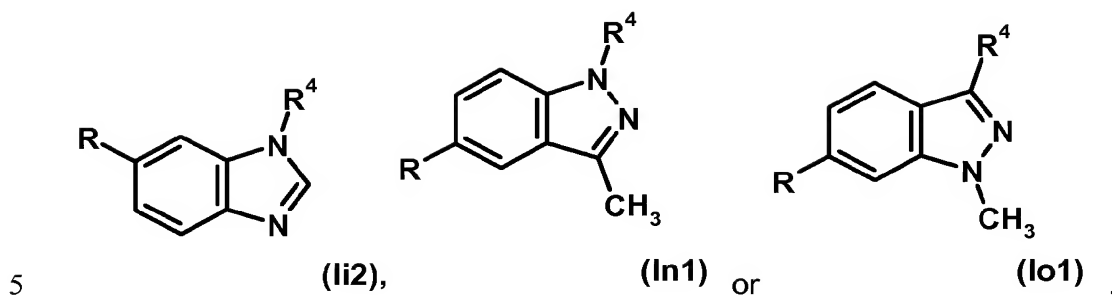
(Ig1),



(Ig2),



(Ii1),



wherein the above-mentioned heterocycles of formulae (la1) and (le1) may each optionally be substituted at the carbon atoms of the 5-ring by a group selected from among C₁₋₂alkyl, trifluoromethylcarbonyl, carboxyl, aminocarbonyl or hydroxymethyl, and

10

wherein the above-mentioned heterocyclic group of formula (lb1) may optionally be substituted at the nitrogen atom of the 5-ring by methyl or hydroxycarbonylmethyl, and wherein

15

R⁴ denotes H, cyano, C₁₋₃-alkyl, phenyl-C₁₋₂-alkyl, phenylsulphonyl-C₁₋₂-alkyl,

C₁₋₃-alkyl-carbonyl, C₁₋₂-alkoxy-carbonyl, phenylcarbonyl, phenyl-C₁₋₂-alkyl-carbonyl, 5-chloro-1H-indol-2-yl-carbonyl,

20

aminocarbonyl, C₁₋₃-alkyl-aminocarbonyl, di-(C₁₋₃-alkyl)-aminocarbonyl, cyclopropyl-aminocarbonyl, N-(cyclopropyl)-N-(C₁₋₂-alkyl)-amino-carbonyl, (N,N-dimethyl-amino)-ethyl-amino-carbonyl, 1-(methylaminocarbonyl)-ethyl-amino-carbonyl, phenylamino-carbonyl, (nitrophenyl)-amino-carbonyl, phenyl-C₁₋₃-alkyl-carbonyl, phenyl-C₁₋₂-alkyl-amino-carbonyl, pyridinylamino-carbonyl, pyrazinylamino-carbonyl, N-oxy-pyridin-3-ylamino-carbonyl,

25

azetidin-1-yl-carbonyl, pyrrolidin-1-yl-carbonyl, 3-hydroxy-pyrrolidin-1-yl-carbonyl, 2-(methylaminocarbonyl)-pyrrolidin-1-yl-carbonyl, piperidin-

30

5 1-yl-carbonyl, morpholin-4-yl-carbonyl, piperazin-1-yl-carbonyl,
 (piperazin-2-on-4-yl)-carbonyl,
 aminocarbonyl-carbonyl, C₁₋₂-alkylaminocarbonyl-carbonyl, di-(C₁₋₂-
 alkyl)-aminocarbonyl-carbonyl, pyrrolidin-1-ylcarbonyl-carbonyl,
 10 benzyl-sulphonyl or phenyl-sulphonyl.

Most particularly preferred are those compounds of the above general formula
 15 I, wherein

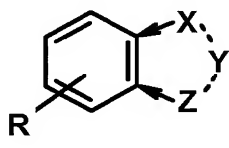
R denotes a group of the above-mentioned formula wherein

20 R¹ denotes H, methyl, ethyl or 2-dimethylamino-ethyl,

R² and R³ independently of one another denote chlorine, ethynyl,
 methoxy, methyl or ethyl and

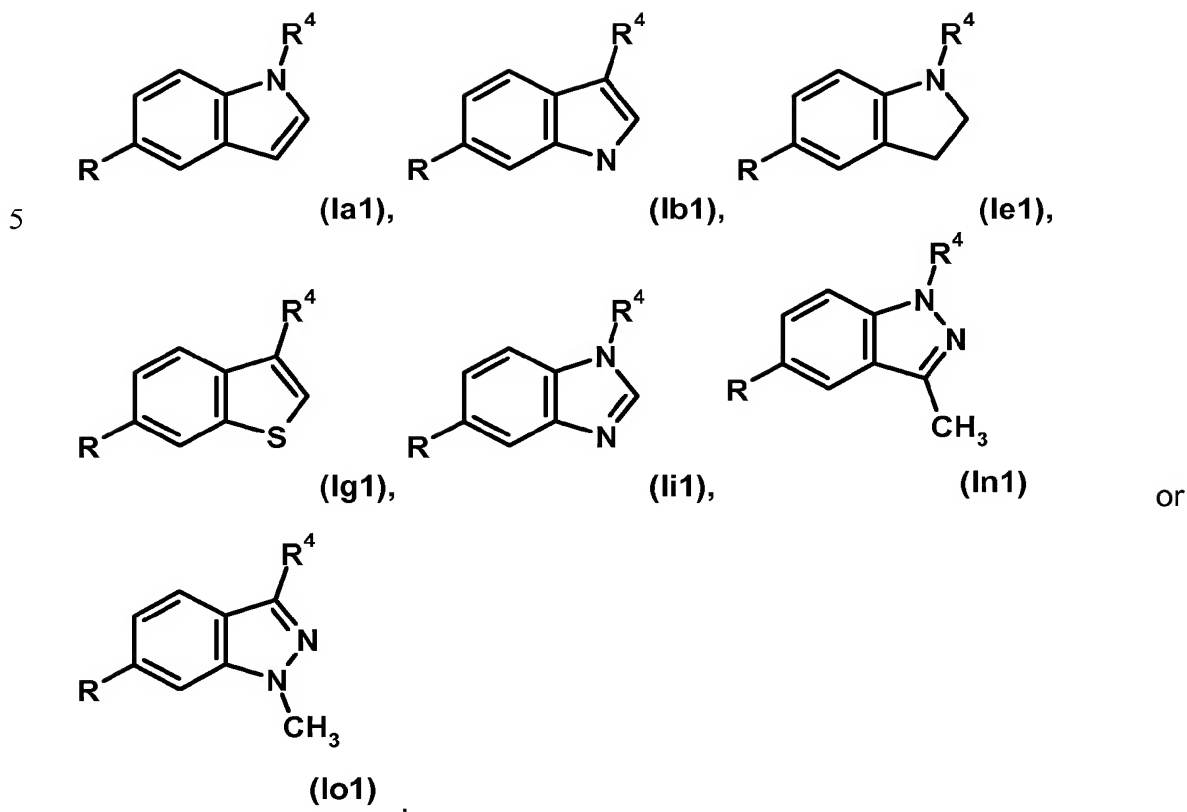
25 A denotes CH or N,

and the heterocyclic group



which may be substituted by R⁴ as hereinbefore described, denotes a group
 of formula

30



10 wherein the above-mentioned heterocyclic group of formula (Ia1) may optionally be substituted by trifluoromethylcarbonyl at the carbon atom of the 5-ring adjacent to the phenyl ring, and

15 wherein the above-mentioned heterocyclic group of formula (Ic1) may optionally be substituted by carboxyl, amino-carbonyl or hydroxymethyl at the carbon atom of the 5-ring adjacent to the phenyl ring, and

20 wherein the above-mentioned heterocyclic group of formula (Ib1) may optionally be substituted by methyl or hydroxycarbonylmethyl at the nitrogen atom of the 5 ring, and wherein

R⁴ denotes H, cyano, ethyl, phenyl-ethyl, phenylsulphonyl-ethyl,

methyl-carbonyl, methoxy-carbonyl, phenylcarbonyl, benzylcarbonyl, 5-

- 5 chloro-1H-indol-2-yl-carbonyl,
- aminocarbonyl, methyl-aminocarbonyl, dimethyl-aminocarbonyl, cyclopropyl-aminocarbonyl, N-(cyclopropyl)-N-(methyl)-aminocarbonyl, (N,N-dimethyl-amino)-ethyl-amino-carbonyl, 1-(methyaminocarbonyl)-ethyl-amino-carbonyl, phenylamino-carbonyl, benzylamino-carbonyl, 3-nitro-phenylamino-carbonyl, 2-nitro-phenylamino-carbonyl, pyridin-3-ylamino-carbonyl, pyridin-4-ylamino-carbonyl, pyrazinylamino-carbonyl, N-oxy-pyridin-3-ylamino-carbonyl,
- 10
- 15 azetidin-1-yl-carbonyl, pyrrolidin-1-yl-carbonyl, 3-hydroxy-pyrrolidin-1-yl-carbonyl, 2-(methyaminocarbonyl)-pyrrolidin-1-yl-carbonyl, piperidin-1-yl-carbonyl, morpholin-4-yl-carbonyl, piperazin-1-yl-carbonyl, (piperazin-2-on-4-yl)-carbonyl,
- 20 aminocarbonyl-carbonyl, methyaminocarbonyl-carbonyl, dimethyl-aminocarbonyl-carbonyl, pyrrolidin-1-ylcarbonyl-carbonyl,
- benzyl-sulphonyl or phenyl-sulphonyl.

25

The following preferred compounds may be mentioned by way of example:

- ~~(1)~~(1) [(3,5-dichloro-phenylsulphonyl)-(1-phenylcarbamoyl-1H-indol-5-yl)-amino]-acetic acid,
- 30 ~~(2)~~(2) [(3,5-dichloro-phenylsulphonyl)-(1-phenylcarbamoyl-2,3-dihydro-1H-indol-5-yl)-amino]-acetic acid,
- ~~(3)~~(3) {(3,5-dichloro-phenylsulphonyl)-[1-(3-nitro-phenylcarbamoyl)-2,3-dihydro-1H-indol-5-yl]-amino}-acetic acid,
- ~~(4)~~(4) {(3,5-dichloro-phenylsulphonyl)-[1-(pyridin-3-ylcarbamoyl)-2,3-dihydro-1H-indol-5-yl]-amino}-acetic acid,
- 35 ~~(5)~~(5) {(3,5-dichloro-phenylsulphonyl)-[1-(2-nitro-phenylcarbamoyl)-2,3-

- 5 dihydro-1H-indol-5-yl]-amino}-acetic acid,
~~(6)~~(6) [(1-acetyl-2,3-dihydro-1H-indol-5-yl)-(3,5-dichloro-phenylsulphonyl)-
amino]-acetic acid,
~~(7)~~(7) [(3,5-dichloro-phenylsulphonyl)-(1-methylcarbamoyl-2,3-dihydro-1H-
indol-5-yl)-amino]-acetic acid,
- 10 ~~(8)~~(8) {(3,5-dichloro-phenylsulphonyl)-[1-(pyridin-4-ylcarbamoyl)-2,3-dihydro-
1H-indol-5-yl]-amino}-acetic acid,
~~(9)~~(9) [(2,6-dichloro-pyridine-4-sulphonyl)-(9-ethyl-9H-carbazol-3-yl)-amino]-
acetic acid,
~~(10)~~(10) {(3,5-dichloro-phenylsulphonyl)-[3-(morpholine-4-carbonyl)-1H-
15 indol-6-yl]-amino}-acetic acid,
~~(11)~~(11) [(3,5-dichloro-phenylsulphonyl)-(3-dimethylcarbamoyl-1-methyl-
1H-indol-6-yl)-amino]-acetic acid,
~~(12)~~(12) [(3,5-dichloro-phenylsulphonyl)-(3-methylcarbamoyl-
benzo[b]thiophen-6-yl)-amino]-acetic acid,
- 20 ~~(13)~~(13) {(3,5-dichloro-phenylsulphonyl)-[1-methyl-3-(pyrrolidine-1-
carbonyl)-1H-indol-6-yl]-amino}-acetic acid,
~~(14)~~(14) [(3,5-dimethyl-phenylsulphonyl)-(1-methylcarbamoyl-2,3-dihydro-
1H-indol-5-yl)-amino]-acetic acid,
~~(15)~~(15) [[3-(azetidine-1-carbonyl)-1-methyl-1H-indol-6-yl]-(3,5-dichloro-
25 phenylsulphonyl)-amino]-acetic acid,
~~(16)~~(16) {(3,5-dichloro-phenylsulphonyl)-[3-(3-hydroxy-pyrrolidine-1-
carbonyl)-1-methyl-1H-indol-6-yl]-amino}-acetic acid,
~~(17)~~(17) [[3-(cyclopropyl-methyl-carbamoyl)-1-methyl-1H-indol-6-yl]-(3,5-
dichloro-phenylsulphonyl)-amino]-acetic acid,
- 30 ~~(18)~~(18) {(3-chloro-5-methyl-phenylsulphonyl)-[1-methyl-3-(pyrrolidine-1-
carbonyl)-1H-indol-6-yl]-amino}-acetic acid,
~~(19)~~(19) {(3,5-dimethyl-phenylsulphonyl)-[1-methyl-3-(pyrrolidine-1-
carbonyl)-1H-indol-6-yl]-amino}-acetic acid and
~~(20)~~(20) [(3,5-dichloro-phenylsulphonyl)-(3-hydroxymethyl-1-
35 methylcarbamoyl-2,3-dihydro-1H-indol-5-yl)-amino]-acetic acid,

5 the enantiomers, the mixtures and the salts thereof.

Some terms used hereinbefore and hereinafter to describe the compounds according to the invention are defined more specifically below.

10 The term halogen denotes an atom selected from among F, Cl, Br and I, particularly F, Cl and Br.

The term C_{1-n} -alkyl, wherein n may have a value as defined hereinbefore or hereinafter, denotes a saturated, branched or unbranched hydrocarbon group with 1 to n C atoms. Examples of such groups include methyl, ethyl, n-propyl, iso-propyl, butyl, iso-butyl, sec-butyl, tert-butyl, n-pentyl, iso-pentyl, neo-pentyl, tert-pentyl, n-hexyl, iso-hexyl, etc..

The term C_{2-n} -alkynyl, wherein n has a value as defined hereinbefore, denotes a branched or unbranched hydrocarbon group with 2 to n C atoms and a $C\equiv C$ triple bond. Examples of such groups include ethynyl, 1-propynyl, 2-propynyl, iso-propynyl, 1-butylnyl, 2-butylnyl, 3-butylnyl, 2-methyl-1-propynyl, 1-pentylnyl, 2-pentylnyl, 3-pentylnyl, 4-pentylnyl, 3-methyl-2-butylnyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, 5-hexynyl etc..

25 The term C_{2-n} -alkenyl, wherein n has a value as defined hereinbefore, denotes a branched or unbranched hydrocarbon group with 2 to n C atoms and a $C=C$ double bond. Examples of such groups include ethenyl, 1-propenyl, 2-propenyl, iso-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-methyl-1-propenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 3-methyl-2-butenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl etc..

The term C_{1-n} -alkoxy or C_{1-n} -alkyloxy denotes a C_{1-n} -alkyl-O group, wherein C_{1-n} -alkyl is as hereinbefore defined. Examples of such groups include methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, iso-butoxy, sec-butoxy, tert-butoxy, n-pentoxy, iso-pentoxy, neo-pentoxy, tert-pentoxy, n-hexoxy, iso-

5 hexoxy etc..

The term C_{1-n}-alkyl-carbonyl denotes a C_{1-n}-alkyl-C(=O) group, wherein C_{1-n}-alkyl is as hereinbefore defined. Examples of such groups include methylcarbonyl, ethylcarbonyl, n-propylcarbonyl, iso-propylcarbonyl, n-
10 butylcarbonyl, iso-butylcarbonyl, sec-butylcarbonyl, tert-butylcarbonyl, n-pentylcarbonyl, iso-pentylcarbonyl, neo-pentylcarbonyl, tert-pentylcarbonyl, n-hexylcarbonyl, iso-hexylcarbonyl, etc..

The term C_{3-n}-cycloalkyl denotes a saturated mono-, bi-, tri- or
15 spirocarbocyclic group with 3 to n C atoms. Examples of such groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclododecyl, bicyclo[3.2.1.]octyl, spiro[4.5]decyl, norpinyl, norbornyl, norcaryl, adamantyl, etc.. Preferably the term C₃₋₇-cycloalkyl includes saturated monocyclic groups.

20 The term C_{3-n}-cycloalkyloxy or C_{3-n}-cycloalkoxy d a C_{3-n}-cycloalkyl-O group, wherein C_{3-n}-cycloalkyl is as hereinbefore defined. Examples of such groups include cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy, cycloheptyloxy, etc..

25 The term C_{1-n}-alkoxy-carbonyl denotes a C_{1-n}-alkyl-O-C(=O) group, wherein C_{1-n}-alkyl is as hereinbefore defined.

The term C_{3-n}-cycloalkyl-carbonyl denotes a C_{3-n}-cycloalkyl-C(=O) group,
30 wherein C_{3-n}-cycloalkyl is as hereinbefore defined.

The terms C_{1-n}-alkyl-amino and di-(C_{1-n}-alkyl)-amino denote a C_{1-n}-alkyl-NH- or a di-(C_{1-n}-alkyl)-N group, respectively, wherein C_{1-n}-alkyl is as hereinbefore defined.

35 The term C_{3-n}-cycloalkyl-amino denotes a C_{3-n}-cycloalkyl-NH group, wherein

5 C_{3-n}-cycloalkyl is as hereinbefore defined.

The term N-(C_{3-n}-cycloalkyl)-N-(C_{1-n}-alkyl)-amino denotes an N-(C_{3-n}-cycloalkyl)-N-(C_{1-n}-alkyl)-N group, wherein C_{3-n}-cycloalkyl and C_{1-n}-alkyl are as hereinbefore defined.

10

The terms C_{1-n}-alkyl-aminocarbonyl and di-(C_{1-n}-alkyl)-aminocarbonyl denote a C_{1-n}-alkyl-NH-C(=O)- or a di-(C_{1-n}-alkyl)-N-C(=O) group, respectively, wherein C_{1-n}-alkyl is as hereinbefore defined.

15 The term C_{3-n}-cycloalkyl-aminocarbonyl denotes a C_{3-n}-cycloalkyl-NH-C(=O) group, wherein C_{3-n}-cycloalkyl is as hereinbefore defined.

The term N-(C_{3-n}-cycloalkyl)-N-(C_{1-n}-alkyl)-amino denotes an N-(C_{3-n}-cycloalkyl)-N-(C_{1-n}-alkyl)-N-C(=O) group, wherein C_{3-n}-cycloalkyl and C_{1-n}-alkyl are as hereinbefore defined.

20

The terms di-(C_{1-n}-alkyl)amino and di-(C_{1-n}-alkyl)aminocarbonyl, wherein n has a value as defined hereinbefore, encompass amino groups which have the same or two different alkyl groups.

25

The term C_{1-n}-perfluoroalkyl denotes a F-(CF₂)_n group. Examples of such groups include trifluoromethyl, pentafluoroethyl, heptafluoro-n-propyl, heptafluoro-iso-propyl etc., but preferably trifluoromethyl, pentafluoroethyl.

30 The term C_{1-n}-perfluoroalkoxy denotes a F-(CF₂)_n-O group. Examples of such groups include trifluoromethoxy, pentafluoroethoxy, heptafluoro-n-propoxy, heptafluoro-iso-propoxy etc., but preferably trifluoromethoxy, pentafluoroethoxy.

35 The term C_{1-n}-alkylsulphonyl denotes a C_{1-n}-alkyl-S(=O)₂ group, wherein C_{1-n}-alkyl is as hereinbefore defined.

5

The compounds according to the invention may be obtained using methods of synthesis that are known in principle. Preferably the compounds are obtained by methods of preparation according to the invention that are described more fully hereinafter.

10

The preparation of compounds of general formula I may be carried out according to Process a) according to the invention shown in Scheme 1, wherein X, Y, Z, R¹, R², R³ and A are as hereinbefore defined, starting from a compound of general formula II.

15

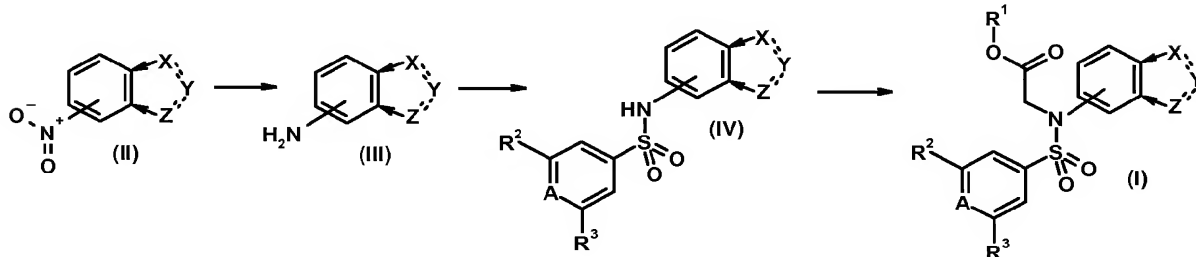


Diagram 1: Process a

20 Here, compounds of general formula III are obtained by reacting a compound of general formula II with a reducing agent. The starting compounds of general formula II or III are either commercially obtainable or may be prepared by synthesising the heterocyclic group and/or nitrogenation (Houben-Weyl, *Methoden der organischen Chemie*, Volume X/1, 463-890) using methods
 25 known *per se* starting from commercially obtainable compounds.

A suitable reducing agent is for example hydrogen in the presence of a catalyst, such as palladium on charcoal, palladium hydroxide on charcoal or Raney nickel, while palladium on charcoal is particularly suitable. The hydrogenation is carried out in a suitable solvent such as methanol, ethanol,
 30 isopropanol, tetrahydrofuran, dichloromethane or ethyl acetate, but preferably methanol, ethanol or tetrahydrofuran, at a pressure between 0.5 and 7 bar, but preferably at a pressure between 0.5 and 3 bar, and at a temperature

- 5 between 0°C and 60°C, but preferably at a temperature between 15°C and 40°C.

Also suitable for the reduction is tin dichloride hydrate in lower alcoholic solvents such as methanol or ethanol at a temperature between ambient temperature and 80°C.

- 10 Alternatively titanium trichloride may be used as reducing agent. Suitable solvents are mixtures of acetone and water. The reaction is carried out between 0°C and 60°C, but preferably between 15°C and 40°C and in the presence of ammonium acetate.

- 15 Compounds of general formula IV are obtained by sulphonylation of compounds of general formula III.

The sulphonylation is carried out with aromatic sulphonyl chlorides in the presence of a base, such as triethylamine, N,N-diisopropyl-N-ethyl-amine, pyridine, or 4-dimethylamino-pyridine, but preferably pyridine. The reaction

- 20 may be carried out in suitable solvents, such as diethyl ether, tetrahydrofuran, toluene, pyridine, dichloromethane, or chloroform, but preferably dichloromethane. The temperature may be between 0°C and 60°C, but preferably between 15°C and 40°C.

- 25 Compounds of general formula I are obtained from compounds of general formula IV by alkylation.

Suitable alkylating agents are acetic acid derivatives that contain a leaving group such as chlorine, bromine, iodine, p-tolylsulphonate, methylsulphonate, or trifluoromethylsulphonate in the 2-position. The alkylation is carried out in a

- 30 solvent such as dimethylformamide, dimethylacetamide, tetrahydrofuran, acetonitrile, N-methylpyrrolidone or dimethylsulphoxide, but preferably in dimethylformamide, in the presence of a base such as sodium carbonate, potassium carbonate or caesium carbonate, but preferably potassium carbonate, and at a temperature between 0°C and 100°C, but preferably
35 between 15°C and 50°C.

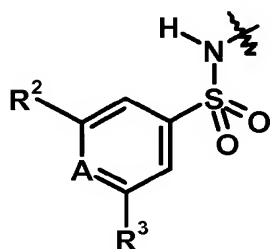
If acetic acid derivatives with a tert.-butyl ester unit are used as alkylating

agents, compounds of general formula I are obtained wherein R^1 = tert.-butyl. The cleaving of the tert.-butyl group is preferably carried out by treatment with an acid such as trifluoroacetic acid or hydrochloric acid or by treatment with iodotrimethylsilane optionally using a solvent such as methylene chloride, dioxane, methanol or diethyl ether.

10

b) Compounds of general formula VI, wherein R^4 is bound to X and X denotes nitrogen, may be obtained by Process b) according to the invention shown in Scheme 2 from compounds of general formula V, wherein $-Y\cdots Z\rightarrow$ has the meaning $-\text{CH}=\text{CH}\rightarrow$, $-\text{CH}_2-\text{CH}_2\rightarrow$ or $-\text{N}=\text{CH}\rightarrow$, but preferably has the meaning $-\text{CH}=\text{CH}\rightarrow$ or $-\text{CH}_2-\text{CH}_2\rightarrow$, while the carbon atoms therein may be substituted as hereinbefore defined and R^4 denotes an acyl, sulphonyl, alkoxy-carbonyl, substituted amino-carbonyl or optionally substituted alkyl group denotes and R^5 denotes the group R defined as hereinbefore, a nitro group or a group of formula

20



wherein R, R^2 , R^3 and A are as hereinbefore defined.

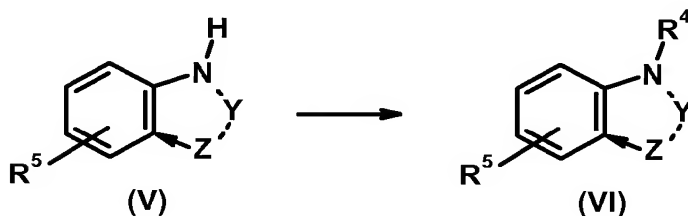


Diagram 2: Process b

25

Acyl groups may be introduced by reacting a compound of general formula V with an acylating reagent such as for example an acid chloride or acid anhydride. The reaction may be carried out in the presence of a base

5 such as sodium hydroxide, sodium hydride, sodium carbonate, potassium carbonate, caesium carbonate, triethylamine or N,N-diisopropyl-N-ethyl-amine as well as in a solvent such as dichloromethane, tetrahydrofuran, dioxane or dimethylformamide at temperatures between -30°C and 200°C, but preferably between 0°C and 160°C. Alternatively the reaction may be carried out by
10 acylation with an acid. For this, the acid is activated in situ by the addition of diisopropylcarbodiimide, dicyclohexylcarbodiimide, N-(3-dimethylaminopropyl)-N'-ethyl-carbodiimide, O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium-tetrafluoroborate (TBTU), O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium-hexafluorophosphate (HBTU), O-(7-azabenzotriazol-1-yl)-
15 N,N,N',N'-tetramethyluronium-hexafluorophosphate (HATU), (benzotriazol-1-yloxy)-tris-(dimethylamino)-phosphonium-hexafluorophosphate (BOP), (benzotriazol-1-yloxy)-tripyrrolidinophosphonium-hexafluorophosphate (PyBOP) and reacted in a dipolar aprotic solvent such as for example N,N-dimethylformamide, dimethylacetamide, tetrahydrofuran, acetonitrile, N-methylpyrrolidone or dimethylsulphoxide, but preferably in N,N-dimethylformamide or N-methylpyrrolidone with a compound of general
20 formula V in the presence of a base such as triethylamine, N,N-diisopropyl-N-ethyl-amine and optionally a catalyst such as 4-N,N-dimethylaminopyridine at temperatures between -20°C and 80°C, but preferably between 0°C and
25 50°C.

Sulphonyl groups may be introduced by reacting with a sulphonyl chloride in the presence of a base such as for example sodium carbonate, potassium carbonate, caesium carbonate, triethylamine or N,N-diisopropyl-N-ethyl-amine, but preferably potassium carbonate, in a solvent such as
30 dichloromethane, tetrahydrofuran, dioxane or N,N-dimethylformamide at temperatures between -30°C and 100°C, but preferably between 0°C and 60°C.

Alkoxycarbonyl groups may be introduced by reacting with an alkyl chloroformate in the presence of a base such as for example sodium
35 carbonate, potassium carbonate, caesium carbonate, triethylamine or N,N-diisopropyl-N-ethyl-amine, but preferably potassium carbonate, in a solvent

- 5 such as dichloromethane, tetrahydrofuran, dioxane or N,N-dimethylformamide at temperatures between -30°C and 100°C, but preferably between 0°C and 60°C. Alternatively, alkoxy carbonyl groups are obtained by reacting a compound of general formula V with phosgene in a solvent such as dichloromethane, tetrahydrofuran or dioxane in the presence of a base such as for example sodium carbonate, potassium carbonate, caesium carbonate, triethylamine or N,N-diisopropyl-N-ethyl-amine, but preferably triethylamine or N,N-diisopropyl-N-ethyl-amine, and subsequently treating with an alcohol at temperatures between -20°C and 100°C, but preferably between 0°C and 50°C.
- 10
- 15 Aminocarbonyl groups may be introduced by reacting with an isocyanate, optionally in the presence of a base such as for example sodium carbonate, potassium carbonate, caesium carbonate, triethylamine or N,N-diisopropyl-N-ethyl-amine in a solvent such as dichloromethane, tetrahydrofuran, dioxane or dimethylformamide at temperatures between -30°C and 150°C, but preferably between 0°C and 100°C. Alternatively aminocarbonyl groups are obtained by reacting a compound of general formula V with phosgene in a solvent such as dichloromethane, tetrahydrofuran or dioxane in the presence of a base such as for example sodium hydride, sodium carbonate, potassium carbonate, caesium carbonate, triethylamine or N,N-diisopropyl-N-ethyl-amine, but preferably sodium hydride, triethylamine or N,N-diisopropyl-N-ethyl-amine and subsequently treating with an amine at temperatures between -20°C and 100°C, but preferably between 0°C and 50°C.
- 20
- 25

In order to introduce alkyl groups the compounds of general formula V are reacted with a base such as for example sodium hydride, potassium hydride, sodium amide, lithium diisopropylamide, lithium hexamethyldisilazide, potassium hexamethyldisilazide or sodium hexamethyldisilazide and an alkylating agent. The reaction is carried out in a solvent such as for example tetrahydrofuran, 1,4-dioxane, dimethylformamide, dimethylacetamide, N-methylpyrrolidone or acetonitrile at temperatures between -40°C and 120°C, but preferably between -10°C and 100°C.

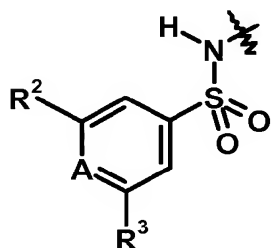
30

35

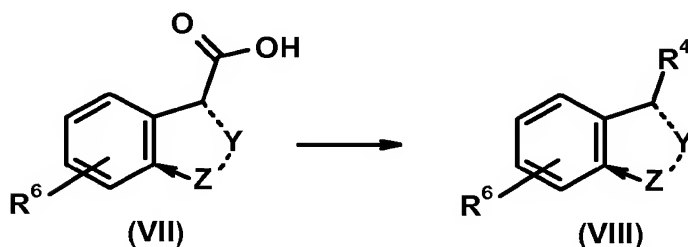
The compounds of general formula VI thus obtained correspond to

intermediates from Scheme 1 and may be converted into the end compounds of general formula I according to Process a).

c) Compounds of general formula VIII, wherein R^4 is bound to X and X denotes a carbon atom or CH, may be obtained according to Process c) according to the invention shown in Scheme 3 from compounds of general formula VII wherein $\cdots Y \cdots Z \rightarrow$ denotes $=CH-N(H)\rightarrow$, $=CH-N(Me)\rightarrow$, $=N-N(Me)\rightarrow$ or $=CH-S\rightarrow$, while the carbon atoms therein may be substituted as hereinbefore defined and R^4 denotes an optionally substituted amino-carbonyl or an alkoxy-carbonyl group and R^6 denotes nitro or



wherein R^2 , R^3 and A are as hereinbefore defined.



Scheme 3: Process c

20

The transformation may be carried out by first converting the acid into an acid chloride. For this, a compound of general formula VII is combined with thionyl chloride, optionally in the presence of a solvent such as toluene or benzene heating it to temperatures between 50°C and 150°C, but preferably between 80°C and 120°C. After the elimination of the volatile constituents the acid chloride thus obtained is reacted with the alcohol or amine in a solvent such as dichloromethane, tetrahydrofuran, dioxane or dimethylformamide, but

25

5 preferably tetrahydrofuran at temperatures between -30°C and 150°C, but preferably between 0°C and 80°C and optionally in the presence of a base such as triethylamine, N,N-diisopropyl-N-ethyl-amine and optionally in the presence of a catalyst such as 4-N,N-dimethylaminopyridine.

Alternatively the acid may be converted into an acid imidazolidine. For this a
10 compound of general formula VII is reacted with carbonyldiimidazole in a solvent such as dichloromethane, tetrahydrofuran or dioxane at temperatures between 20°C and 100°C. The acid imidazolidine thus obtained is reacted with the alcohol or amine in a solvent such as dichloromethane, tetrahydrofuran, dioxane or dimethylformamide, but preferably tetrahydrofuran, at
15 temperatures between -30°C and 150°C, but preferably between 0°C and 80°C, and optionally in the presence of a base such as triethylamine, N,N-diisopropyl-N-ethyl-amine and optionally in the presence of a catalyst such as 4-N,N-dimethylaminopyridine.

Moreover, compounds of general formula VIII may be prepared by in situ
20 activation of the carboxylic acid. For this, the acid is activated by the addition of diisopropylcarbodiimide, dicyclohexylcarbodiimide, N-(3-dimethylaminopropyl)-N'-ethyl-carbodiimide, O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium-tetrafluoroborate (TBTU), O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium-hexafluorophosphate (HBTU), O-(7-azabenzotriazol-1-yl)-
25 N,N,N',N'-tetramethyluronium-hexafluorophosphate (HATU), (benzotriazol-1-yloxy)-tris-(dimethylamino)-phosphonium-hexafluorophosphate (BOP), (benzotriazol-1-yloxy)-tripyrrolidinophosphonium-hexafluorophosphate (PyBOP) and reacted in a dipolar aprotic solvent such as for example dimethylformamide, dimethylacetamide, tetrahydrofuran, acetonitrile, N-
30 methylpyrrolidone or dimethylsulphoxide, but preferably in dimethylformamide or N-methylpyrrolidone, with an alcohol or an amine in the presence of a base such as triethylamine, N,N-diisopropyl-N-ethyl-amine and optionally a catalyst such as 4-N,N-dimethylaminopyridine at temperatures between -20°C and 80°C, but preferably between 0°C and 50°C.

35 Compounds of general formula VIII wherein R⁴ denotes alkoxy-carbonyl may also be prepared by alkylating carboxylic acids of general formula VII. For

5 this, the carboxylic acid is reacted with an alkylating agent. Suitable alkylating agents are alkyl derivatives that contain a leaving group such as chlorine, bromine, iodine, p-tolylsulphonate, methylsulphonate or trifluoromethylsulphonate. The alkylation is carried out in a solvent such as dimethylformamide, dimethylacetamide, tetrahydrofuran, acetonitrile, N-
10 methylpyrrolidone or dimethylsulphoxide, but preferably in dimethylformamide, in the presence of a base such as sodium carbonate, potassium carbonate or caesium carbonate, but preferably potassium carbonate, at a temperature between 0°C and 100°C, but preferably between 15°C and 50°C. The compounds of general formula VIII thus obtained correspond to inter-
15 mediates from Scheme 1 and may be converted into the end compounds of general formula I according to Process a).

d) Compounds of general formula III, wherein Y and Z are as hereinbefore defined and X denotes a group of formula $-C(R^4)=$, wherein R^4 is an
20 alkylcarbonyl or arylcarbonyl group optionally substituted as mentioned hereinbefore, may be obtained by Process d) from compounds of general formula III, wherein Y and Z are as hereinbefore defined and X denotes a group of formula $-CH=$.

25 For this a compound of general formula III, wherein Y and Z are as hereinbefore defined and X denotes a group of formula $-CH=$, is reacted with an acid chloride or an acid anhydride, but preferably an acid anhydride. The reaction may be carried out without a solvent or with a solvent such as for example dichloromethane, 1,2-dichloroethane, toluene, tetrahydrofuran, 1,4-
30 dioxane, dimethylformamide, dimethylacetamide or N-methyl-pyrrolidone and optionally in the presence of a catalyst such as for example aluminium trichloride or boron trifluoride etherate and at temperatures between -10°C and 180°C, but preferably between 0°C and 120°C. The compounds thus obtained correspond to intermediates from Scheme 1
35 and and may be converted into the end compounds of general formula I according to Process a).

5

- e) Compounds of general formula III, wherein Y and Z are as hereinbefore defined and X denotes a group of formula $-C(R^4)=$, wherein R^4 denotes an aminocarbonyl or alkoxycarbonyl group optionally substituted as mentioned hereinbefore, may be obtained by Process e) from compounds of general formula III, wherein Y and Z are as hereinbefore defined and X denotes a group of formula $-C(CF_3)=$.

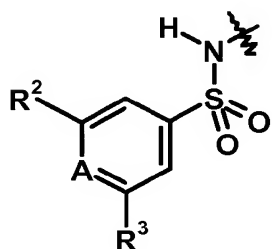
The compounds of general formula III, wherein Y and Z are as hereinbefore defined and X denotes a group of formula $-C(CF_3)=$, are reacted with 5 to 50 %, but preferably 40 % sodium hydroxide solution or potassium hydroxide solution at temperatures between 0°C and 200°C, but preferably between ambient temperature and 150°C. The carboxylic acids of general formula III thus obtained, wherein Y and Z are as hereinbefore defined and X denotes a group of formula $-C(COOH)=$, may for example be converted into an acid chloride.

For this the carboxylic acid obtained as described hereinbefore may be combined with thionyl chloride, optionally in the presence of a solvent such as toluene or benzene, and heated to temperatures between 50°C and 150°C, but preferably between 80°C and 120°C. After elimination of the volatile constituents the acid chloride thus obtained is reacted with the alcohol or amine in a solvent such as dichloromethane, tetrahydrofuran, dioxane or dimethylformamide, but preferably tetrahydrofuran at temperatures between -30°C and 150°C, but preferably between 0°C and 80°C and optionally in the presence of a base such as triethylamine, N,N-diisopropyl-N-ethyl-amine and optionally in the presence of a catalyst such as 4-N,N-dimethylaminopyridine. Alternatively the acid may be converted into an acid imidazolid. For this a compound of general formula III, wherein Y and Z are as hereinbefore defined and X denotes a group of formula $-C(COOH)=$ is reacted with carbonyldiimidazole in a solvent such as dichloromethane, tetrahydrofuran or dioxane at temperatures between 20°C and 100°C. The acid imidazolid thus obtained is reacted with the alcohol or amine in a solvent such as

- 5 dichloromethane, tetrahydrofuran, dioxane or dimethylformamide, but preferably tetrahydrofuran, at temperatures between -30°C and 150°C, but preferably between 0°C and 80°C, and optionally in the presence of a base such as triethylamine, N,N-diisopropyl-N-ethylamine and optionally in the presence of a catalyst such as 4-N,N-dimethylaminopyridine.
- 10 Moreover, compounds of general formula III, wherein Y and Z are as hereinbefore defined and X denotes a group of formula $-C(R^4)=$, where R^4 denotes an aminocarbonyl or alkoxycarbonyl group optionally substituted as mentioned hereinbefore, are prepared by in situ activation of the carboxylic acid. For this the acid is activated by the addition of diisopropylcarbodiimide, dicyclohexylcarbodiimide, N-(3-dimethylaminopropyl)-N'-ethyl-carbodiimide,
- 15 O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium-tetrafluoroborate (TBTU), O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium-hexafluorophosphate (HBTU), O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium-hexafluorophosphate (HATU), (benzotriazol-1-yloxy)-tris-(dimethylamino)-
- 20 phosphonium-hexafluorophosphate (BOP), (benzotriazol-1-yloxy)-tripyrrolidinophosphonium-hexafluorophosphate (PyBOP) and reacted in a dipolar aprotic solvent such as for example dimethylformamide, dimethylacetamide, tetrahydrofuran, acetonitrile, N-methylpyrrolidone or dimethylsulphoxide, but preferably in dimethylformamide or N-
- 25 methylpyrrolidone, with an alcohol or amine in the presence of a base such as triethylamine, N,N-diisopropyl-N-ethyl-amine and optionally a catalyst such as 4-N,N-dimethylaminopyridine at temperatures between -20°C and 80°C, but preferably between 0°C and 50°C.
- Compounds of general formula III, wherein Y and Z are as hereinbefore
- 30 defined and X denotes a group of formula $-C(R^4)=$, where R^4 denotes an alkoxycarbonyl group optionally substituted as mentioned hereinbefore, may also be prepared by alkylation of carboxylic acids of general formula VII. For this the carboxylic acid is reacted with an alkylating agent. Suitable alkylating agents are alkyl derivatives that contain a leaving group such as chlorine,
- 35 bromine, iodine, p-tolylsulphonate, methylsulphonate or trifluoromethylsulphonate. The alkylation is carried out in a solvent such as

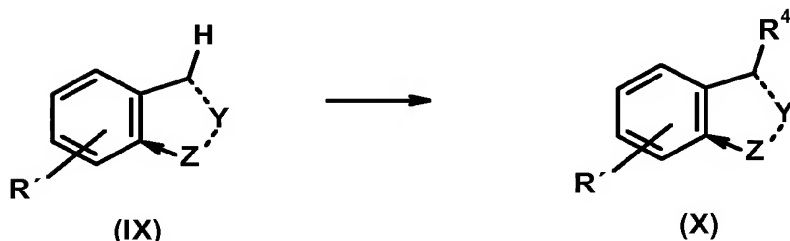
- 5 dimethylformamide, dimethylacetamide, tetrahydrofuran, acetonitrile, N-methylpyrrolidone or dimethylsulphoxide, but preferably in dimethylformamide, in the presence of a base such as sodium carbonate, potassium carbonate or caesium carbonate, but preferably potassium carbonate, at a temperature between 0°C and 100°C, but preferably between 15°C and 50°C.
- 10 The compounds thus obtained correspond to intermediates from Scheme 1 and may be converted into the end compounds of general formula I according to Process a).

- Compounds of general formula X wherein X and Y are defined as stated
- 15 hereinafter and R^4 denotes an aminocarbonyl-carbonyl group, may be obtained by Process f) shown in Scheme 4 from compounds of general formula IX wherein $\cdots Y \cdots Z \rightarrow$ has the meaning $=CH-N(H)\rightarrow$, $=CH-N(Me)\rightarrow$, $=N-N(Me)\rightarrow$ or $=CH-S\rightarrow$ where the carbon atoms therein may be substituted as hereinbefore defined, and R' denotes nitro or



20

wherein R^2 , R^3 and A are as hereinbefore defined.



25

Diagram 4: Process f

5

In this, compounds of general formula IX are converted into the chloro-carbonyl-carbonyl derivatives by reaction with oxalyl chloride in a solvent such as dichloromethane, diethyl ether, tetrahydrofuran, dioxane or toluene, but preferably diethyl ether, at temperatures between -20°C and 80°C, but preferably between 0°C and 50°C. After elimination of the volatile constituents they are reacted with an amine in a solvent such as dichloromethane, tetrahydrofuran, dioxane or dimethylformamide, but preferably tetrahydrofuran, at temperatures between -30°C and 70°C, but preferably between 0°C and 50°C and optionally in the presence of a base such as triethylamine, N,N-diisopropyl-N-ethyl-amine and optionally in the presence of a catalyst such as 4-N,N-dimethylaminopyridine to form the compounds of general formula X.

The compounds of general formula X thus obtained correspond to intermediates from Scheme 1 and may be converted according to Process a) into the end compounds of general formula I.

Cyano functionalities may in each case be prepared from primary amides obtained in the syntheses. Suitable methods for this transformation are, for example, reaction with thionyl chloride and optionally catalytic amounts of dimethylformamide in a solvent such as dichloromethane, 1,2-dichloroethane, toluene or acetone at temperatures between 0°C and 100°C, reaction with trifluoroacetic anhydride or trichloroacetic anhydride, a base such as for example pyridine, triethylamine or N,N-diisopropyl-N-ethyl-amine in a solvent such as for example dichloromethane, 1,2-dichloroethane, tetrahydrofuran, 1,4-dioxane or toluene at temperatures between -10°C and 100°C, as well as reaction with phosphorus oxychloride and optionally a base such as pyridine or N,N-dimethylaniline in the presence or absence of a solvent such as for example dichloromethane, 1,2-dichloroethane, tetrahydrofuran, 1,4-dioxane or toluene, at temperatures between -10°C and 120°C.

35

Sulphonyl chlorides may be prepared from anilines. For this, the aniline is

- 5 first diazotised by reacting with sodium nitrite in hydrochloric acid at temperatures between -30°C and 10°C . The diazonium salt solution thus prepared is then added dropwise to copper-II-chloride and water in a 30% sulphur dioxide solution in glacial acetic acid at temperatures between -30°C and 10°C . Then it is left to warm up to temperatures between 5°C and 50°C .
- 10 Alternatively the sulphonyl chlorides may be prepared from aryl metal compounds such as aryl lithium or aryl magnesium chloride compounds. Aryl lithium compounds are obtained from the aryl bromides or aryl iodides by reacting with n-butyllithium, sec-butyllithium or tert.-butyllithium in a solvent such as diethyl ether or tetrahydrofuran at temperatures between
- 15 -60°C and -85°C . Arylmagnesium chloride compounds are obtained by a process as described in *Angew. Chem.* **2006**, 118, 3024-3027. The aryl metal compounds thus obtained are further reacted at temperatures between -78°C and -20°C by piping sulphur dioxide through. This produces metal sulphinates, which can optionally be precipitated by the addition of hexane.
- 20 The metal sulphinates are dissolved in dichloromethane and combined with N-chlorosuccinimide at temperatures between -20°C and 30°C . After the reaction the solid is filtered off, to obtain a dichloromethane solution of the sulphonyl chloride.
- 25 In the reactions described hereinbefore, any reactive groups present such as carboxy, hydroxy, amino or alkylamino groups may be protected during the reaction by conventional protecting groups which are cleaved again after the reaction.
- 30 For example, a protecting group for a carboxy group may be a methyl, ethyl, tert.butyl or benzyl group.

For example, a protecting group for a hydroxy group may be an acetyl, benzyl or tetrahydropyranyl group.

- 35 Protecting groups for an amino or alkylamino may be a formyl, acetyl,

- 5 trifluoroacetyl, ethoxycarbonyl, tert.butoxycarbonyl, benzyloxycarbonyl, benzyl, methoxybenzyl or 2,4-dimethoxybenzyl group.

A carboxymethyl or carboxyethyl unit is cleaved for example by hydrolysis in an aqueous solvent, e.g. In water, methanol/water, isopropanol/water, acetic
10 acid/water, tetrahydrofuran/water or dioxane/water, but preferably in methanol/water, in the presence of an acid such as trifluoroacetic acid, hydrochloric acid or sulphuric acid or in the presence of an alkali metal base such as lithium hydroxide, sodium hydroxide or potassium hydroxide, but preferably sodium hydroxide, or aprotically, e.g. In the presence of
15 iodotrimethylsilane, at temperatures between 0 and 120°C, preferably at temperatures between 10 and 100°C.

A benzyl, methoxybenzyl or benzyloxycarbonyl group is advantageously cleaved by hydrogenolysis, e.g. with hydrogen in the presence of a catalyst
20 such as palladium on charcoal in a suitable solvent such as methanol, ethanol, ethyl acetate or glacial acetic acid, optionally with the addition of an acid such as hydrochloric acid, at temperatures between 0 and 100°C, but preferably at temperatures between 20 and 60°C, and under a hydrogen pressure of 1 to 7 bar, but preferably 1 to 3 bar. However, a 2,4-dimethoxy-
25 benzyl group is preferably cleaved in trifluoroacetic acid in the presence of anisole.

A tert.-butyl or tert.-butoxycarbonyl group is preferably cleaved by treating with an acid such as trifluoroacetic acid or hydrochloric acid or by treating with
30 iodotrimethylsilane, optionally using a solvent such as methylene chloride, dioxane, methanol or diethyl ether.

Moreover, the compounds of general formula I obtained, or intermediate products from the synthesis of compounds of general formula I, as already
35 mentioned hereinbefore, may be resolved into their enantiomers and/or diastereomers. Thus, for example, cis/trans mixtures may be resolved into

- 5 their cis and trans isomers, and compounds with at least one stereocentre may be resolved into their enantiomers.

Thus, for example, the cis/trans mixtures may be resolved by chromatography into the cis and trans isomers thereof, the compounds of general formula I
10 obtained, or intermediate products from the synthesis of compounds of general formula I, which occur as racemates may be separated by methods known per se (cf. Allinger N. L. And Eliel E. L. In "Topics in Stereochemistry", Vol. 6, Wiley Interscience, 1971) into their optical antipodes and compounds of general formula I, or intermediate products from the
15 synthesis of compounds of general formula I, with at least 2 asymmetric carbon atoms may be resolved into their diastereomers on the basis of their physical-chemical differences using methods known per se, e.g. by chromatography and/or fractional crystallisation, and, if these compounds are obtained in racemic form, they may subsequently be resolved into the
20 enantiomers as mentioned above.

The enantiomers are preferably separated by chromatography on chiral phases or by recrystallisation from an optically active solvent or by reacting with an optically active substance which forms salts or derivatives such as
25 e.g. Esters or amides with the racemic compound, particularly acids and the activated derivatives or alcohols thereof, and separating the diastereomeric mixture of salts or derivatives thus obtained, e.g. on the basis of their differences in solubility, whilst the free antipodes may be released from the pure diastereomeric salts or derivatives by the action of suitable agents.

30 Optically active acids in common use are e.g. The D- and L-forms of tartaric acid or dibenzoyltartaric acid, di-O-p-toluoyltartaric acid, malic acid, mandelic acid, camphorsulphonic acid, glutamic acid, aspartic acid or quinic acid. An optically active alcohol may be for example (+) or (-)-menthol and an optically active acyl group in amides, for example, may be a (+)-or
35 (-)-menthyloxycarbonyl.

5 Furthermore, the compounds of formula I obtained, or intermediate products from the synthesis of compounds of general formula I, may be converted into the salts thereof, particularly for pharmaceutical use into the physiologically acceptable salts thereof with inorganic or organic acids. Acids which may be used for this purpose include for example hydrochloric acid, hydrobromic acid,
10 sulphuric acid, methanesulphonic acid, phosphoric acid, fumaric acid, succinic acid, lactic acid, citric acid, tartaric acid or maleic acid.

Moreover, the new compounds of general formula I obtained, or intermediate products from the synthesis of compounds of general formula I, if they contain
15 a carboxy group, may subsequently, if desired, be converted into the salts thereof with inorganic or organic bases, particularly for pharmaceutical use into the physiologically acceptable salts thereof. Suitable bases for this purpose include for example sodium hydroxide, potassium hydroxide, arginine, cyclohexylamine, ethanolamine, diethanolamine and
20 triethanolamine.

The compounds of general formula I are inhibitors of the interaction between human liver glycogen phosphorylase (HLGP) and protein PPP1R3 (G_L-subunit of glycogen-associated protein phosphatase 1 (PP1)). The effect of
25 the compounds on the binding of the protein PPP1R3 and the glycogen phosphorylase activated by phosphorylation is determined in a binding test based on SPA technology (Amersham Pharmacia). The binding of the substances inhibits the interaction of the glycogen phosphorylase with the protein PPP1R3B. All measurements were made in triplicate in the 384-well
30 format (Optiplat, Perkin Elmer).

Human glycogen phosphorylase is recombinantly expressed in E. Coli and purified. The isolated non-phosphorylated HLGP is radioactively labelled in a marking reaction with phosphorylase kinase (200-500 U/ mg, P2014, Sigma) and ³³P-gamma ATP (110 TBq/ mmol, Hartmann Analytic) (Ref.: Cohen et
35 al., Methods Enzymol. 1988, Vol 159 pp 390). In a binding test, in a volume of 100 µl (test buffer: 50 mM Tris/HCl pH 7.0, 0.1 mM EGTA, 0.1% mercapto-

- 5 ethanol), different amounts of a test substance (final concentration: 1 nM to 30 μ M) are incubated at ambient temperature for 16 hours with 100000 cpm of labelled HLGP, 375 μ g streptavidin-SPA Beads (RPNQ 0007, Amersham Pharmacia), 0.1 μ g GL-peptide (Biotin-FPEWPSYLGYEKLGPYY). After centrifuging for 5 minutes at 500 g the plate is measured (Topcount, Packard).
- 10 The cpm values measured are used to calculate the IC_{50} values specified. The basal value is determined in the absence of the peptide and the maximum value is determined in the absence of the test substance.

The compounds of general formula I have IC_{50} values in the range from 100
15 nM to 15 μ M.

- In view of their ability to suppress the interaction of glycogen phosphorylase a with the GL-subunit of glycogen-associated protein phosphatase 1 (PP1), the compounds of general formula I according to the invention and the
- 20 corresponding pharmaceutically acceptable salts thereof are theoretically suitable for treating and/or preventatively treating all those conditions or diseases that can be influenced by inhibiting the interaction of glycogen phosphorylase a with the GL-subunit of glycogen-associated protein phosphatase 1 (PP1). Therefore the compounds according to the invention
- 25 are particularly suitable for the prevention or treatment of diseases, particularly metabolic disorders, or conditions such as type 1 and type 2 diabetes mellitus, complications of diabetes (such as e.g. retinopathy, nephropathy or neuropathies, diabetic foot, ulcers, macroangiopathies), metabolic acidosis or ketosis, reactive hypoglycaemia, hyperinsulinaemia,
- 30 glucose metabolic disorder, insulin resistance, metabolic syndrome, dyslipidaemias of different origins, atherosclerosis and related diseases, obesity, high blood pressure, chronic heart failure, oedema and hyperuricaemia. These substances are also suitable for preventing beta-cell degeneration such as e.g. Apoptosis or necrosis of pancreatic beta cells.
- 35 The substances are also suitable for improving or restoring the functionality of pancreatic cells, and also for increasing the number and size of pancreatic

5 beta cells. The compounds according to the invention may also be used as diuretics or antihypertensives and are suitable for the prevention and treatment of acute renal failure.

10 In particular, the compounds according to the invention, including the physiologically acceptable salts thereof, are suitable for the prevention or treatment of diabetes, particularly type 1 and type 2 diabetes mellitus, and/or diabetic complications.

15 The dosage required to achieve the corresponding activity for treatment or prevention usually depends on the compound which is to be administered, the patient, the nature and gravity of the illness or condition and the method and frequency of administration and is for the patient's doctor to decide.

20 Expediently, the dosage may be from 0.1 to 1000 mg, preferably 0.5 to 500 mg, by intravenous route, and 1 to 1000 mg, preferably 10 to 500 mg, by oral route, in each case administered 1 to 4 times a day. For this purpose, the compounds of formula I prepared according to the invention may be formulated, optionally together with other active substances, together with one or more inert conventional carriers and/or diluents, e.g. with corn starch, lactose, glucose, microcrystalline cellulose, magnesium stearate,
25 polyvinylpyrrolidone, citric acid, tartaric acid, water, water/ethanol, water/glycerol, water/sorbitol, water/polyethylene glycol, propylene glycol, cetylstearyl alcohol, carboxymethylcellulose or fatty substances such as hard fat or suitable mixtures thereof, to produce conventional galenic preparations such as plain or coated tablets, capsules, powders, suspensions or
30 suppositories.

35 The compounds according to the invention may also be used in conjunction with other active substances, particularly for the treatment and/or prevention of the diseases and conditions mentioned above. Other active substances which are suitable for such combinations include in particular those which potentiate the therapeutic effect of an inhibitor of the interaction of glycogen

5 phosphorylase a with the G_L subunit of glycogen-associated protein
phosphatase 1 (PP1) according to the invention with respect to one of the
indications mentioned and/or which allow the dosage of an an inhibitor of the
interaction of glycogen phosphorylase a with the G_L subunit of glycogen-
associated protein phosphatase 1 (PP1) according to the invention to be
10 reduced. Therapeutic agents which are suitable for such a combination
include, for example, antidiabetic agents such as metformin, sulphonylureas
(e.g. glibenclamide, tolbutamide, glimepiride), nateglinide, repaglinide,
thiazolidinediones (e.g. rosiglitazone, pioglitazone), PPAR-gamma-agonists
(e.g. GI 262570) and antagonists, PPAR-gamma/alpha modulators (e.g. KRP
15 297), alpha-glucosidase inhibitors (e.g. miglitol, acarbose, voglibose), DPPIV
inhibitors (e.g. sitagliptine, vildagliptine), SGLT2-inhibitors, alpha2-
antagonists, insulin and insulin analogues, GLP-1 and GLP-1 analogues (e.g.
Exendin-4) or amylin. Other active substances suitable as combination
partners are inhibitors of protein tyrosinephosphatase 1, substances that
20 affect deregulated glucose production in the liver, such as e.g. Inhibitors of
glucose-6-phosphatase, or fructose-1,6-bisphosphatase, glycogen
phosphorylase, glucagon receptor antagonists and inhibitors of phosphoenol
pyruvate carboxykinase, glycogen synthase kinase or pyruvate
dehydrokinase, lipid lowering agents such as for example HMG-CoA-
25 reductase inhibitors (e.g. simvastatin, atorvastatin), fibrates (e.g. bezafibrate,
fenofibrate), nicotinic acid and the derivatives thereof, PPAR-alpha agonists,
PPAR-delta agonists, ACAT inhibitors (e.g. Avasimibe) or cholesterol
absorption inhibitors such as, for example, ezetimibe, bile acid-binding
substances such as, for example, cholestyramine, inhibitors of ileac bile acid
30 transport, HDL-raising compounds such as CETP inhibitors or ABC1
regulators or active substances for treating obesity, such as sibutramine or
tetrahydrolipostatin, dexfenfluramine, axokine, antagonists of the
cannabinoid1 receptor, MCH-1 receptor antagonists, MC4 receptor agonists,
NPY5 or NPY2 antagonists or β 3-agonists such as SB-418790 or AD-9677
35 and agonists of the 5HT_{2c} receptor.

5 Moreover, combinations with drugs for influencing high blood pressure, chronic heart failure or atherosclerosis such as e.g. A-II antagonists or ACE inhibitors, ECE inhibitors, diuretics, β -blockers, Ca-antagonists, centrally acting antihypertensives, antagonists of the alpha-2-adrenergic receptor, inhibitors of neutral endopeptidase, thrombocyte aggregation inhibitors and
10 others or combinations thereof are suitable. Examples of angiotensin II receptor antagonists are candesartan cilexetil, potassium losartan, eprosartan mesylate, valsartan, telmisartan, irbesartan, EXP-3174, L-158809, EXP-3312, olmesartan, medoxomil, tasosartan, KT-3-671, GA-0113, RU-64276, EMD-90423, BR-9701, etc. Angiotensin II receptor antagonists are preferably used
15 for the treatment or prevention of high blood pressure and complications of diabetes, often combined with a diuretic such as hydrochlorothiazide.

A combination with uric acid synthesis inhibitors or uricosurics is suitable for the treatment or prevention of gout.

20

A combination with GABA-receptor antagonists, Na-channel blockers, topiramate, protein-kinase C inhibitors, advanced glycation end product inhibitors or aldose reductase inhibitors may be used for the treatment or prevention of complications of diabetes.

25

The dosage for the combination partners mentioned above is usefully 1/5 of the lowest dose normally recommended up to 1/1 of the normally recommended dose.

30 Therefore, in another aspect, this invention relates to the use of a compound according to the invention or a physiologically acceptable salt of such a compound combined with at least one of the active substances described above as a combination partner, for preparing a pharmaceutical composition which is suitable for the treatment or prevention of diseases or conditions
35 which can be affected by inhibiting the interaction of glycogen phosphorylase a with the G_L subunit of glycogen-associated protein phosphatase 1 (PP1).

- 5 These are preferably metabolic diseases, particularly one of the diseases or conditions listed above, most particularly diabetes or diabetic complications.

The use of the compound according to the invention, or a physiologically acceptable salt thereof, in combination with another active substance may
10 take place simultaneously or at staggered times, but particularly within a short space of time. If they are administered simultaneously, the two active substances are given to the patient together; if they are used at staggered times the two active substances are given to the patient within a period of less than or equal to 12 hours, but particularly less than or equal to 6 hours.

15 Consequently, in another aspect, this invention relates to a pharmaceutical composition which comprises a compound according to the invention or a physiologically acceptable salt of such a compound and at least one of the active substances described above as combination partners, optionally
20 together with one or more inert carriers and/or diluents.

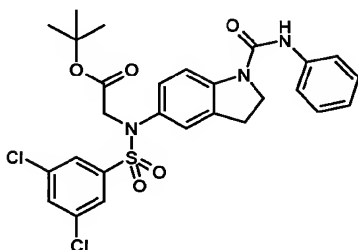
Thus, for example, a pharmaceutical composition according to the invention comprises a combination of a compound of formula I according to the invention or a physiologically acceptable salt of such a compound and at least
25 one angiotensin II receptor antagonist optionally together with one or more inert carriers and/or diluents.

The compound according to the invention, or a physiologically acceptable salt thereof, and the additional active substance to be combined therewith may
30 both be present together in one formulation, for example a tablet or capsule, or separately in two identical or different formulations, for example as a so-called kit-of-parts.

In the foregoing and following text, H atoms of oxygen and nitrogen atoms are
35 not explicitly shown in every case in structural formulae. The Examples that follow are intended to illustrate the present invention without restricting it:

5 Preparation of the starting compounds:

Example I



10 tert. butyl [(3,5-dichloro-phenylsulphonyl)-(1-phenylcarbamoyl-2,3-dihydro-1H-indol-5-yl)-amino]-acetate

990 mg tert. butyl [(3,5-dichloro-phenylsulphonyl)-(2,3-dihydro-1H-indol-5-yl)-amino]-acetate are dissolved in 10 ml dichloromethane. 598 mg potassium carbonate and 247 μ l phenylisocyanate are added. After stirring overnight the solid is filtered off and washed twice with dichloromethane. The combined organic phases are evaporated down in vacuo and the residue is purified by chromatography on silica gel (cyclohexane/ethyl acetate 10:1 to 1:2).

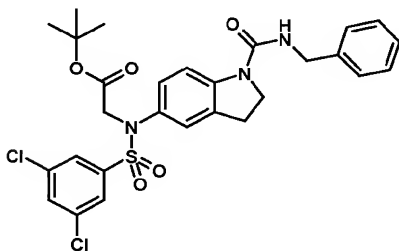
Yield: 1.24 g (99 % of theory)

Mass spectrum (ESI⁺): m/z = 576 [M+H]⁺

20

The following compounds are obtained analogously to Example I:

(1) tert. butyl [(1-benzylcarbamoyl-2,3-dihydro-1H-indol-5-yl)-(3,5-dichloro-phenylsulphonyl)-amino]-acetate



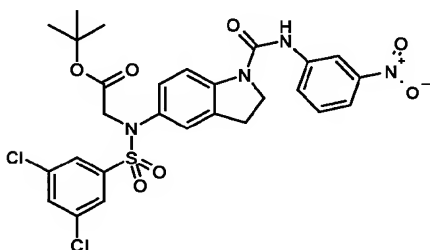
25

Carried out without potassium carbonate for 3 hours.

Mass spectrum (ESI⁺): m/z = 589 [M+H]⁺

5

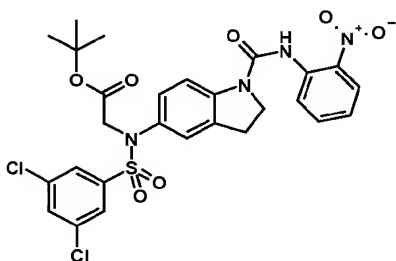
(2) tert. butyl {(3,5-dichloro-phenylsulphonyl)-[1-(3-nitro-phenylcarbamoyl)-2,3-dihydro-1H-indol-5-yl]-amino}-acetate



Carried out for 3 hours. Then the mixture is divided between water and ethyl acetate. The aqueous phase is extracted with ethyl acetate. The combined organic phases are dried on sodium sulphate, the solvents are eliminated in vacuo, and the residue is extracted from diisopropylether.

Mass spectrum (ESI⁺): m/z = 621 [M+H]⁺

15 (3) tert. butyl {(3,5-dichloro-phenylsulphonyl)-[1-(2-nitro-phenylcarbamoyl)-2,3-dihydro-1H-indol-5-yl]-amino}-acetate

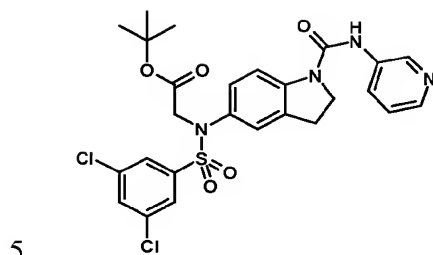


Carried out for 3 hours. The mixture is diluted with ethyl acetate and washed successively with dilute citric acid solution and saturated sodium chloride solution. After drying with magnesium sulphate the solvents are eliminated in vacuo and the residue is extracted from diethyl ether. The solid is filtered off. The mother liquor is evaporated down in vacuo, and the residue is purified by chromatography on silica gel.

Mass spectrum (ESI⁺): m/z = 621 [M+H]⁺

25

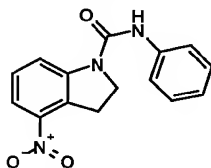
(4) tert. butyl {(3,5-dichloro-phenylsulphonyl)-[1-(pyridin-3-ylcarbamoyl)-2,3-dihydro-1H-indol-5-yl]-amino}-acetate



Carried out for 3 hours. The mixture is diluted with ethyl acetate and washed successively with dilute citric acid solution and saturated sodium chloride solution. After drying with magnesium sulphate the solvents are eliminated in vacuo.

10 Mass spectrum (ESI⁺): m/z = 577 [M+H]⁺

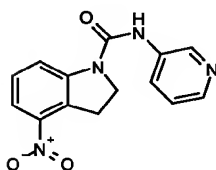
(5) 4-nitro-2,3-dihydro-indole-1-carboxylic acid-phenylamide



15 After the reaction the mixture is diluted with dichloromethane and washed twice with saturated sodium chloride solution. Then it is dried on magnesium sulphate, the solvents are eliminated in vacuo and the residue is extracted from diisopropylether.

Mass spectrum (ESI⁺): m/z = 284 [M+H]⁺

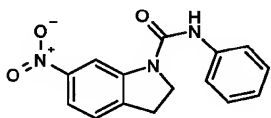
20 (6) 4-nitro-2,3-dihydro-indole-1-carboxylic acid-pyridin-3-ylamide



After the reaction the mixture is diluted with dichloromethane and washed twice with saturated sodium chloride solution. Then it is dried on magnesium sulphate and the solvent is eliminated in vacuo.

25 Mass spectrum (ESI⁺): m/z = 285 [M+H]⁺

5 (7) 6-nitro-2,3-dihydro-indole-1-carboxylic acid-phenylamide

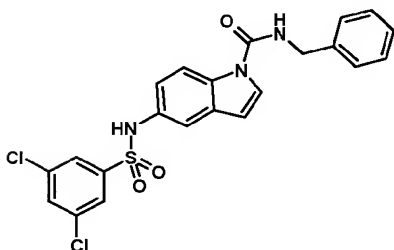


After the reaction the mixture is diluted with dichloromethane and washed with semi-saturated sodium chloride solution. Then it is dried on magnesium sulphate and the solvent is eliminated in vacuo. The residue is

10 chromatographed on silica gel.

Mass spectrum (ESI⁺): m/z = 284 [M+H]⁺

Example II



15

5-(3,5-dichloro-phenylsulphonylamino)-indole-1-carboxylic acid-benzylamide

130 mg 3,5-dichloro-N-(1H-indol-5-yl)-phenylsulphonamide are dissolved in 5 ml dichloromethane and 14 mg dimethylaminopyridine and 56 µl benzyliocyanate are added. The mixture is stirred overnight at ambient temperature, divided between 1 N HCl and ethyl acetate, the aqueous phase is extracted with ethyl acetate and the combined organic phases are dried with magnesium sulphate. The solvents are eliminated in vacuo and the residue is chromatographed on silica gel (cyclohexane/ethyl acetate 10:1 to 1:3).

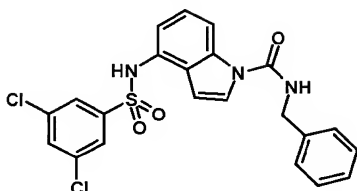
25 Yield: 152 mg (84 % of theory)

Mass spectrum (ESI⁺): m/z = 474 [M+H]⁺

The following compounds are obtained analogously to Example II:

30 (1) 4-(3,5-dichloro-phenylsulphonylamino)-indole-1-carboxylic acid-

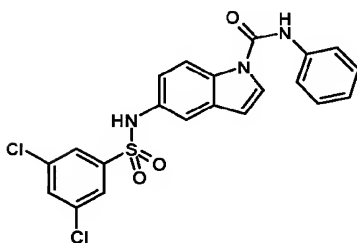
5 benzylamide



Mass spectrum (ESI⁺): m/z = 474 [M+H]⁺

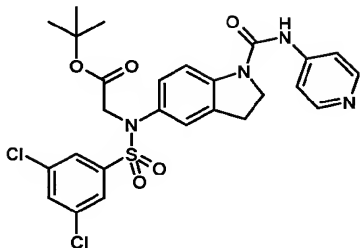
Example III

10

5-(3,5-dichloro-phenylsulphonylamino)-indole-1-carboxylic acid-phenylamide

- 100 mg 3,5-dichloro-N-(1H-indol-5-yl)-phenylsulphonamide are dissolved in 3 ml dimethylformamide. 38 μ l phenylisocyanate and 10 dimethylaminopyridine are added and the mixture is heated to 80°C for 5 minutes in the microwave. Then another 30 μ l phenylisocyanate are added and the mixture is heated to 100°C for 15 minutes in the microwave. The solvent is then eliminated in vacuo and the residue is chromatographed on silica gel (cyclohexane/ethyl acetate 10:1 to 1:3).
- Yield: 124 mg (the product also contains 3,5-dichloro-N-(1H-indol-5-yl)-phenylsulphonamide and diphenylurea)
- Mass spectrum (ESI⁻): m/z = 458 [M-H]⁻

25

5 Example IV

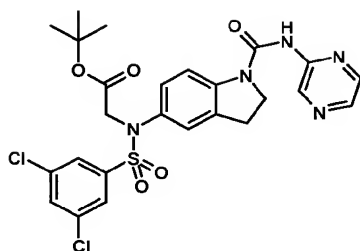
tert. butyl {(3,5-dichloro-phenylsulphonyl)-[1-(pyridin-4-ylcarbamoyl)-2,3-dihydro-1H-indol-5-yl]-amino}-acetate

- 10 215 mg tert. butyl [(3,5-dichloro-phenylsulphonyl)-(2,3-dihydro-1H-indol-5-yl)-amino]-acetate are dissolved in 10 ml dichloromethane. For this 75 μ l diisopropylethylamine and 1 ml of a 20 % solution of phosgene in toluene are added. The mixture is stirred for another 2 hours and then the solvents are eliminated in a nitrogen current. The residue is taken up in 10 ml of
- 15 tetrahydrofuran. To this is added a solution prepared by the addition of 75 mg 4-aminopyridine to a solution of 30 mg sodium hydride (60 % suspension in mineral oil) in 10 ml of tetrahydrofuran and 30 minutes' stirring. The mixture is stirred overnight at ambient temperature and then refluxed for 24 hours. The solvents are eliminated in vacuo and the residue is purified by
- 20 chromatography on silica gel (cyclohexane/ethyl acetate 10:1 to 1:3).
Yield: 190 mg (70 % of theory)
Mass spectrum (ESI⁺): m/z = 577 [M+H]⁺

The following compounds are obtained analogously to Example IV:

25

(1) tert. butyl {(3,5-dichloro-phenylsulphonyl)-[1-(pyrazin-2-ylcarbamoyl)-2,3-dihydro-1H-indol-5-yl]-amino}-acetate



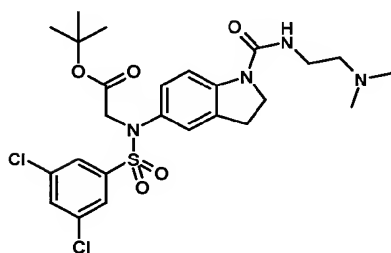
5

Carried out for 2 hours at ambient temperature.

Mass spectrum (ESI⁺): m/z = 578 [M+H]⁺

Example V

10



tert. butyl {(3,5-dichloro-phenylsulphonyl)-[1-(2-dimethylamino-ethylcarbamoyl)-2,3-dihydro-1H-indol-5-yl]-amino}-acetate

800 µl of a 20 % solution of phosgene in toluene are dissolved in 10 ml
 15 dichloromethane and cooled to 0°C . To this are added 35 µl
 diisopropylethylamine and 100 mg tert. butyl [(3,5-dichloro-phenylsulphonyl)-
 (2,3-dihydro-1H-indol-5-yl)-amino]-acetate. The mixture is stirred for a further
 1 hour and then the solvents are eliminated in a nitrogen current. The residue
 is taken up in 10 ml of tetrahydrofuran, 200 µl N,N-dimethylethylenediamine
 20 are added and the mixture is stirred for 3 hours at ambient temperature. Then
 it is diluted with ethyl acetate and washed with semi-saturated sodium
 chloride solution. The organic phase is dried on magnesium sulphate, the
 solvents are eliminated in vacuo and the residue is purified by
 25 chromatography on aluminium oxide (cyclohexane/ethyl acetate 3:7 to ethyl
 acetate).

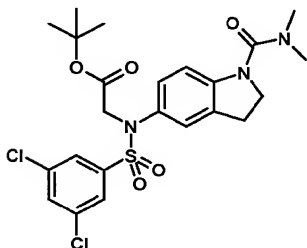
Yield: 75 mg (60 % of theory)

Mass spectrum (ESI⁺): m/z = 571 [M+H]⁺

5

The following compounds are obtained analogously to Example V:

(1) tert. butyl [(3,5-dichloro-phenylsulphonyl)-(1-dimethylcarbamoyl-2,3-dihydro-1H-indol-5-yl)-amino]-acetate

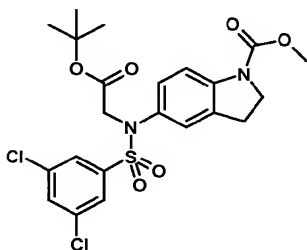


10

Carried out for 3 hours at 60°C.

Mass spectrum (ESI⁺): m/z = 528 [M+H]⁺

(2) methyl 5-[tert-butoxycarbonylmethyl-(3,5-dichloro-phenylsulphonyl)-amino]-2,3-dihydro-indole-1-carboxylate



15

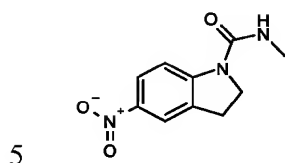
4-Pyridylamine is used instead of N,N-dimethylethylenediamine. Carried out overnight at ambient temperature. Then the solvents are eliminated in vacuo, the residue is taken up in methanol and purified by chromatography on silica gel. It is not the desired product 5-[tert-butoxycarbonylmethyl-(3,5-dichloro-phenylsulphonyl)-amino]-2,3-dihydro-indole-1-carboxylic acid-pyridin-3-yl-amide, but methyl 5-[tert-butoxycarbonylmethyl-(3,5-dichloro-phenylsulphonyl)-amino]-2,3-dihydro-indole-1-carboxylate that is isolated.

20

Mass spectrum (ESI⁺): m/z = 532 [M+NH₄]⁺

25

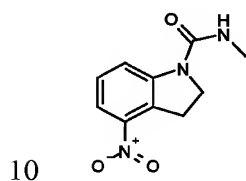
(3) 5-nitro-2,3-dihydro-indole-1-carboxylic acid-methylamide



The crude product is extracted from 1 N HCl.

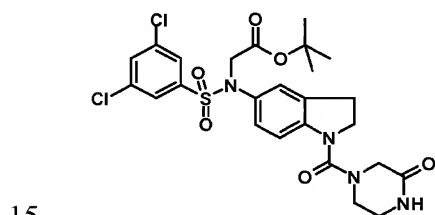
Mass spectrum (ESI⁺): m/z = 222 [M+H]⁺

(4) 4-nitro-2,3-dihydro-indole-1-carboxylic acid-methylamide



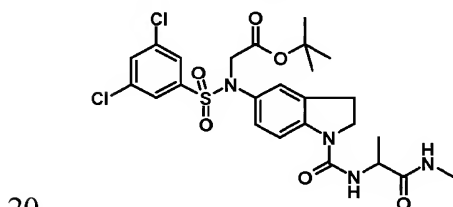
Mass spectrum (ESI⁺): m/z = 222 [M+H]⁺

(5) tert. butyl (3,5-dichloro-phenylsulphonyl)-[1-(3-oxo-piperazin-1-carbonyl)-2,3-dihydro-1H-indol-5-yl]-amino}-acetate



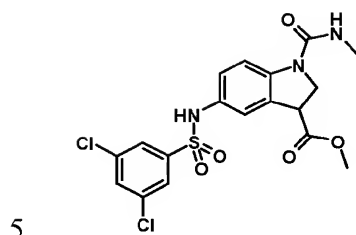
Mass spectrum (ESI⁺): m/z = 600 [M+NH₄]⁺

(6) tert. butyl {(3,5-dichloro-phenylsulphonyl)-[1-(1-methylcarbamoyl-ethylcarbamoyl)-2,3-dihydro-1H-indol-5-yl]-amino}-acetate



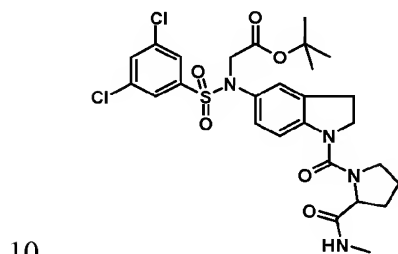
Mass spectrum (ESI⁺): m/z = 585 [M+H]⁺

(7) methyl 5-(3,5-dichloro-phenylsulphonylamino)-1-methylcarbamoyl-2,3-dihydro-1H-indole-3-carboxylate



Mass spectrum (ESI⁺): m/z = 458 [M+H]⁺

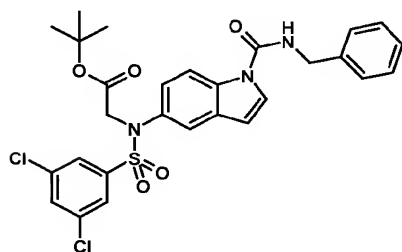
(8) tert. butyl {(3,5-dichloro-phenylsulphonyl)-[1-(2-methylcarbamoyl-pyrrolidine-1-carbonyl)-2,3-dihydro-1H-indol-5-yl]-amino}-acetate



Mass spectrum (ESI⁺): m/z = 611 [M+H]⁺

Example VI

15



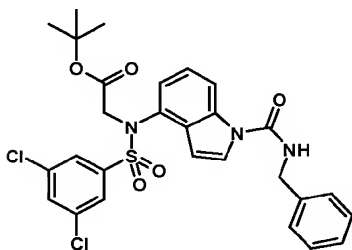
tert. butyl [(1-benzylcarbamoyl-1H-indol-5-yl)-(3,5-dichloro-phenylsulphonyl)-amino]-acetate

150 mg 5-(3,5-dichloro-phenylsulphonylamino)-indole-1-carboxylic acid-
 20 benzylamide are dissolved in 5 ml dimethylformamide. 109 mg potassium carbonate and 51 µl tert. butyl bromoacetate are added thereto. The mixture is stirred for 4 hours at ambient temperature, the solvent is eliminated in vacuo and the residue is divided between water and ethyl acetate. The

- 5 aqueous phase is extracted with ethyl acetate and the combined organic phases are dried on magnesium sulphate. The solvents are eliminated in vacuo and the residue is purified by chromatography on silica gel (cyclohexane/ethyl acetate 10:1 to 1:3).
Yield: 127 mg (68 % of theory)
- 10 Mass spectrum (ESI⁻): m/z = 586 [M-H]⁻

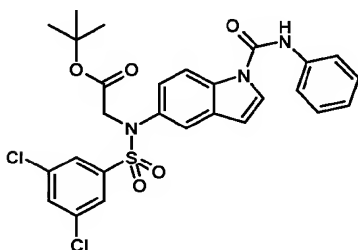
The following compounds are obtained analogously to Example VI:

- (1) tert. butyl [(1-benzylcarbamoyl-1H-indol-4-yl)-(3,5-dichloro-phenylsulphonyl)-amino]-acetate
- 15



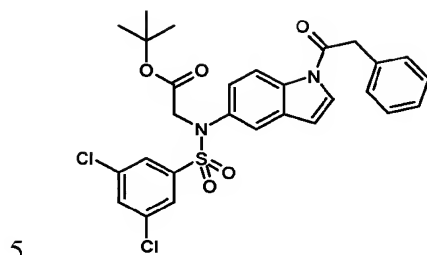
Mass spectrum (ESI⁻): m/z = 586 [M-H]⁻

- (2) tert. butyl [(3,5-dichloro-phenylsulphonyl)-(1-phenylcarbamoyl-1H-indol-5-yl)-amino]-acetate
- 20



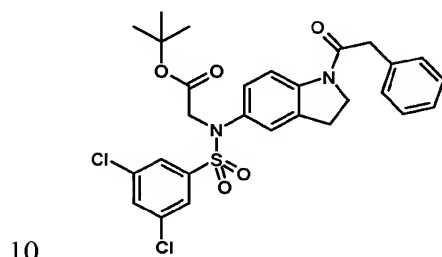
The product is further reacted directly in Example 1 (3).

- (3) tert. butyl [(3,5-dichloro-phenylsulphonyl)-(1-phenylacetyl-1H-indol-5-yl)-amino]-acetate
- 25



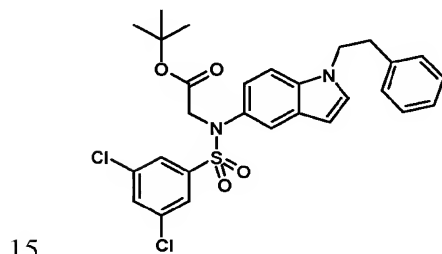
Mass spectrum (ESI⁺): m/z = 590 [M+NH₄]⁺

(4) tert. butyl [(3,5-dichloro-phenylsulphonyl)-(1-phenylacetyl-2,3-dihydro-1H-indol-5-yl)-amino]-acetate



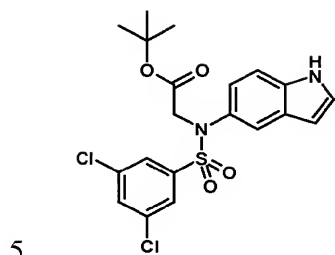
Mass spectrum (ESI⁺): m/z = 575 [M+H]⁺

(5) tert. butyl
{(3,5-dichloro-phenylsulphonyl)-[1-(phenylethyl)-1H-indol-5-yl]-amino}-acetate



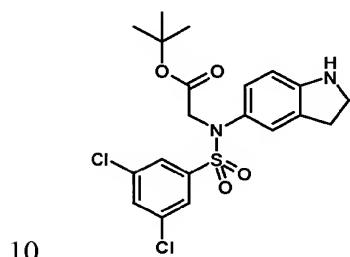
Mass spectrum (ESI⁺): m/z = 576 [M+NH₄]⁺

(6) tert. butyl [(3,5-dichloro-phenylsulphonyl)-(1H-indol-5-yl)-amino]-acetate



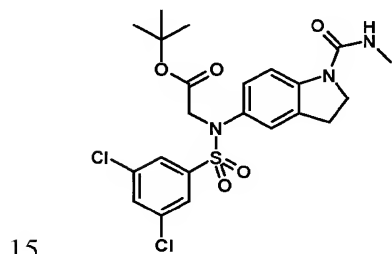
Mass spectrum (ESI⁺): m/z = 472 [M+NH₄]⁺

(7) tert. butyl [(3,5-dichloro-phenylsulphonyl)-(2,3-dihydro-1H-indol-5-yl)-amino]-acetate



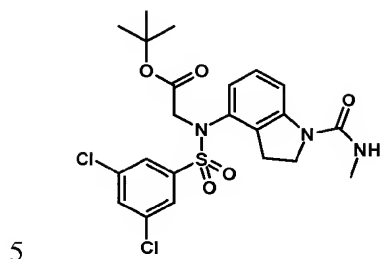
Mass spectrum (ESI⁺): m/z = 455 [M-H]⁺

(8) tert. butyl [(3,5-dichloro-phenylsulphonyl)-(1-methylcarbamoyl-2,3-dihydro-1H-indol-5-yl)-amino]-acetate



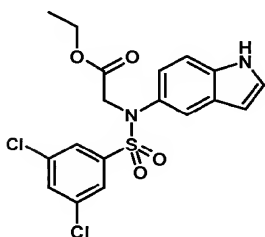
Mass spectrum (ESI⁺): m/z = 514 [M+H]⁺

(9) tert. butyl [(3,5-dichloro-phenylsulphonyl)-(1-methylcarbamoyl-2,3-dihydro-1H-indol-4-yl)-amino]-acetate



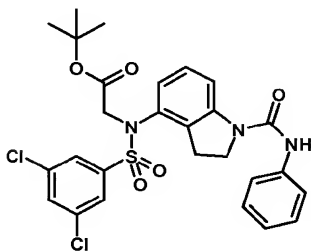
Mass spectrum (ESI⁺): m/z = 514 [M+H]⁺

(10) ethyl [(3,5-dichloro-phenylsulphonyl)-(1H-indol-5-yl)-amino]-acetate



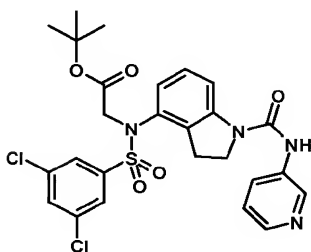
10 Mass spectrum (ESI⁺): m/z = 427 [M+H]⁺

(11) tert. butyl [(3,5-dichloro-phenylsulphonyl)-(1-phenylcarbamoyl-2,3-dihydro-1H-indol-4-yl)-amino]-acetate



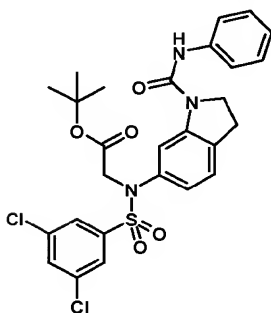
15 Mass spectrum (ESI⁺): m/z = 576 [M+H]⁺

(12) tert. butyl {(3,5-dichloro-phenylsulphonyl)-[1-(pyridin-3-ylcarbamoyl)-2,3-dihydro-1H-indol-4-yl]-amino}-acetate



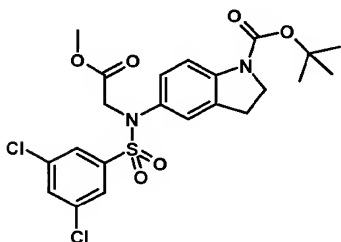
- 5 Mass spectrum (ESI⁺): m/z = 577 [M+H]⁺

(13) tert. butyl [(3,5-dichloro-phenylsulphonyl)-(1-phenylcarbamoyl-2,3-dihydro-1H-indol-6-yl)-amino]-acetate



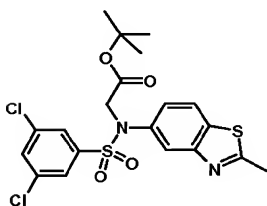
- 10 Mass spectrum (ESI⁺): m/z = 576 [M+H]⁺

(14) tert-butyl 5-[(3,5-dichloro-phenylsulphonyl)-methoxycarbonylmethyl-amino]-2,3-dihydro-indole-1-carboxylate



- 15 Mass spectrum (ESI⁺): m/z = 532 [M+NH₄]⁺

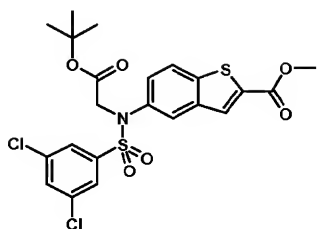
(15) tert. butyl [(3,5-dichloro-phenylsulphonyl)-(2-methyl-benzothiazole-5-yl)-amino]-acetate



- 20 Mass spectrum (ESI⁺): m/z = 487 [M+H]⁺

(16) methyl 5-[tert-butoxycarbonylmethyl-(3,5-dichloro-phenylsulphonyl)-amino]-benzo[b]thiophen-2-carboxylate

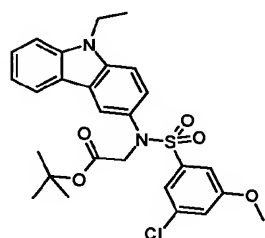
5



Mass spectrum (ESI⁺): m/z = 547 [M+NH₄]⁺

(17) tert. butyl [(3-chloro-5-methoxy-phenylsulphonyl)-(9-ethyl-9H-carbazol-3-yl)-amino]-acetate

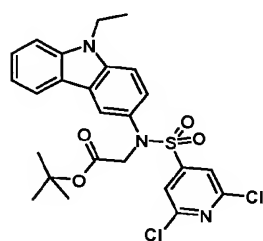
10



Mass spectrum (ESI⁺): m/z = 529 [M+H]⁺

(18) tert. butyl [(2,6-dichloro-pyridine-4-sulphonyl)-(9-ethyl-9H-carbazol-3-yl)-amino]-acetate

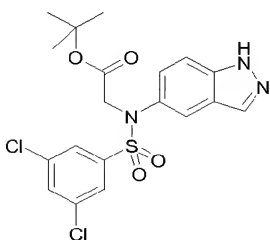
15



Mass spectrum (ESI⁺): m/z = 534 [M+H]⁺

(19) tert. butyl [(3,5-dichloro-phenylsulphonyl)-(1H-indazol-5-yl)-amino]-acetate

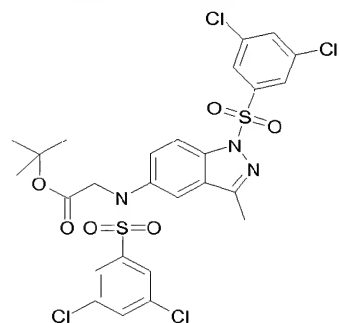
20



5 Mass spectrum (ESI⁺): m/z = 294 [M+H]⁺

R_f value: 0.53 (silica gel: ethyl acetate/petroleum ether 1:1)

(20) tert. butyl {(3,5-dichloro-phenylsulphonyl)-[1-(3,5-dichloro-phenylsulphonyl)-3-methyl-1H-indazol-5-yl]-amino}-acetate



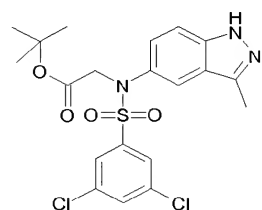
10

This is isolated as a by-product of the formation of VI (21) from XI (13).

Mass spectrum (ESI⁺): m/z = 678 [M+H]⁺

R_f value: 0.80 (silica gel: petroleum ether/ethyl acetate 2:1)

15 (21) tert. butyl [(3,5-dichloro-phenylsulphonyl)-(3-methyl-1H-indazol-5-yl)-amino]-acetate

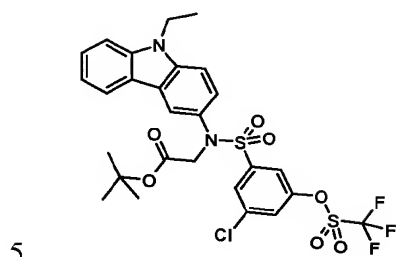


Mass spectrum (ESI⁺): m/z = 470 [M+H]⁺

R_f value: 0.32 (silica gel: petroleum ether/ethyl acetate 2:1)

20

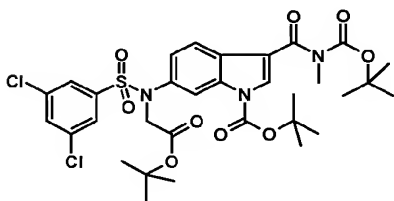
(22) tert-butyl [(3-chloro-5-trifluoromethylsulphonyloxy-phenylsulphonyl)-(9-ethyl-9H-carbazol-3-yl)-amino]-acetate



Mass spectrum (ESI⁺): m/z = 664 [M+NH₄]⁺

(23) tert-butyl 3-(tert-butoxycarbonyl-methyl-aminocarbonyl)-6-[tert-butoxycarbonylmethyl-(3,5-dichloro-phenylsulphonyl)-amino]-indole-1-carboxylate

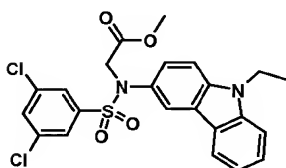
10



Mass spectrum (ESI⁺): m/z = 712 [M+H]⁺

(24) methyl [(3,5-dichloro-phenylsulphonyl)-(9-ethyl-9H-carbazol-3-yl)-amino]-acetate

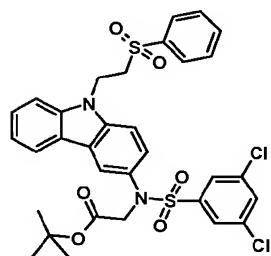
15



The product is further reacted directly in Example 6.

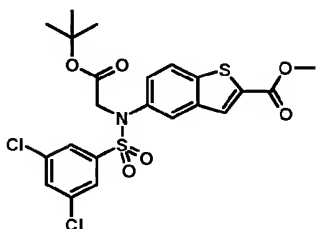
(25) tert. butyl [[9-(2-phenylsulphonyl-ethyl)-9H-carbazol-3-yl]-(3,5-dichloro-phenylsulphonyl)-amino]-acetate

20



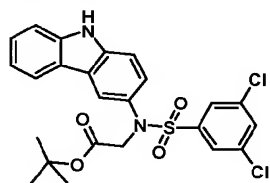
- 5 Mass spectrum (ESI^+): $m/z = 690$ $[\text{M}+\text{NH}_4]^+$

(26) methyl 5-[tert-butoxycarbonylmethyl-(3,5-dichloro-phenylsulphonyl)-amino]-benzo[b]thiophen-2-carboxylate



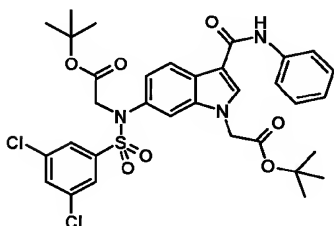
- 10 Mass spectrum (ESI^+): $m/z = 547$ $[\text{M}+\text{NH}_4]^+$

(27) tert. butyl [(9H-carbazol-3-yl)-(3,5-dichloro-phenylsulphonyl)-amino]-acetate



- 15 Mass spectrum (ESI^-): $m/z = 503$ $[\text{M}-\text{H}]^-$

(28) tert. butyl {6-[tert-butoxycarbonylmethyl-(3,5-dichloro-phenylsulphonyl)-amino]-3-phenylcarbamoyl-indol-1-yl}-acetate

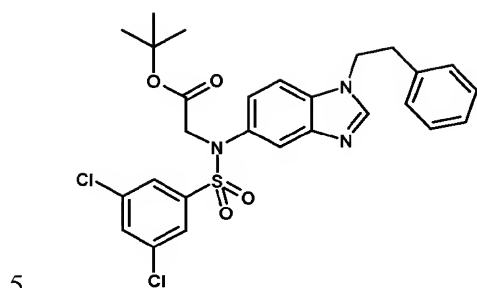


- 20 Obtained from the reaction of 6-(3,5-dichloro-phenylsulphonylamino)-1H-indole-3-carboxylic acid-phenylamide.

The product is further reacted directly in 1 (38).

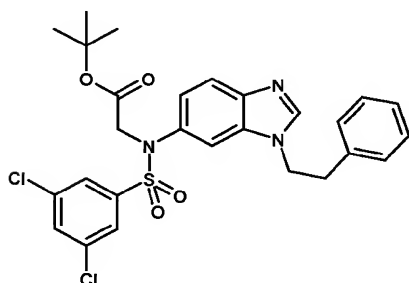
(29) tert. butyl {(3,5-dichloro-phenylsulphonyl)-[1-(phenylethyl)-1H-

- 25 benzoimidazol-5-yl]-amino}-acetate



and

tert. butyl {(3,5-dichloro-phenylsulphonyl)-[3-(phenylethyl)-3H-benzoimidazol-5-yl]-amino}-acetate



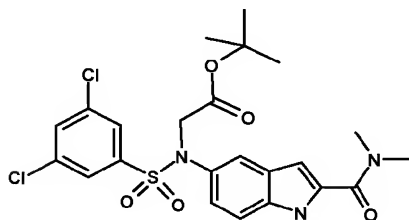
- 10 Obtained from the reaction of a mixture of 3,5-dichloro-N-(1-phenylethyl-1H-benzoimidazol-5-yl)-phenylsulphonamide and 3,5-dichloro-N-[3-(phenylethyl)-3H-benzoimidazol-5-yl]-phenylsulphonamide. The products may be separated by chromatography on silica gel.

Mass spectrum (ESI⁺): m/z = 560 [M+H]⁺ tert. butyl {(3,5-dichloro-

- 15 phenylsulphonyl)-[1-(phenylethyl)-1H-benzoimidazol-5-yl]-amino}-acetate and
Mass spectrum (ESI⁺): m/z = 560 [M+H]⁺ tert. butyl {(3,5-dichloro-phenylsulphonyl)-[3-(phenylethyl)-3H-benzoimidazol-5-yl]-amino}-acetate

(30) tert. butyl [(3,5-dichloro-phenylsulphonyl)-(2-dimethylcarbamoyl-1H-indol-5-yl)-amino]-acetate

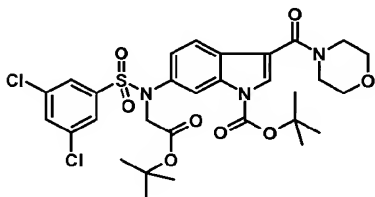
- 20



Mass spectrum (ESI⁺): m/z = 526 [M+H]⁺

5

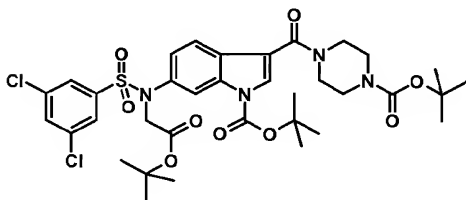
(31) tert-butyl 6-[tert-butoxycarbonylmethyl-(3,5-dichloro-phenylsulphonyl)-amino]-3-(morpholine-4-carbonyl)-indole-1-carboxylate



Mass spectrum (ESI⁺): m/z = 668 [M+H]⁺

10

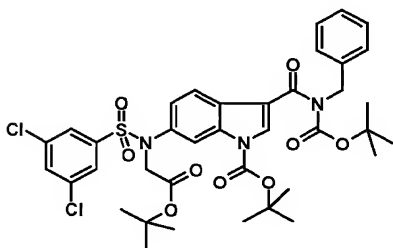
(32) tert-butyl 6-[tert-butoxycarbonylmethyl-(3,5-dichloro-phenylsulphonyl)-amino]-3-(4-tert-butoxycarbonyl-piperazin-1-carbonyl)-indole-1-carboxylate



Mass spectrum (ESI⁺): m/z = 767 [M+H]⁺

15

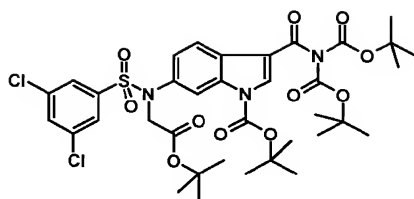
(33) tert-butyl 3-(benzyl-tert-butoxycarbonyl-aminocarbonyl)-6-[tert-butoxycarbonylmethyl-(3,5-dichloro-phenylsulphonyl)-amino]-indole-1-carboxylate



20 Mass spectrum (ESI⁺): m/z = 788 [M+H]⁺

(34) tert-butyl 3-(bis-tert-butoxycarbonyl)-aminocarbonyl-6-[tert-butoxycarbonylmethyl-(3,5-dichloro-phenylsulphonyl)-amino]-indole-1-carboxylate

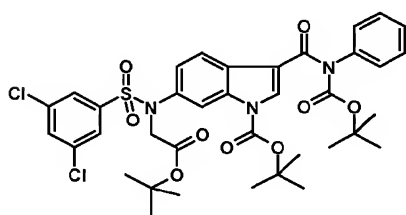
5



Mass spectrum (ESI⁺): m/z = 798 [M+H]⁺

(35) tert-butyl 6-[tert-butoxycarbonylmethyl-(3,5-dichloro-phenylsulphonyl)-amino]-3-(tert-butoxycarbonyl-phenyl-aminocarbonyl)-indole-1-carboxylate

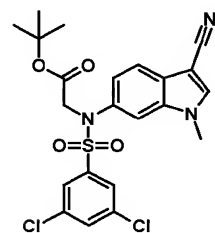
10



Mass spectrum (ESI⁺): m/z = 774 [M+H]⁺

(36) tert-butyl [(3-cyano-1-methyl-1H-indol-6-yl)-(3,5-dichloro-phenylsulphonyl)-amino]-acetate

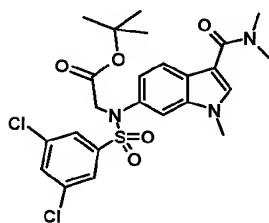
15



Mass spectrum (ESI⁺): m/z = 511 [M+NH₄]⁺

(37) tert-butyl [(3,5-dichloro-phenylsulphonyl)-(3-dimethylcarbamoyl-1-methyl-1H-indol-6-yl)-amino]-acetate

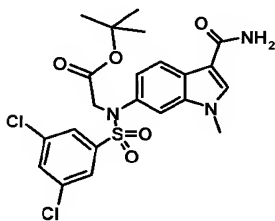
20



Mass spectrum (ESI⁺): m/z = 540 [M+H]⁺

5

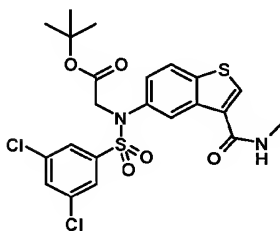
(38) tert. butyl [(3-carbamoyl-1-methyl-1H-indol-6-yl)-(3,5-dichloro-phenylsulphonyl)-amino]-acetate



Mass spectrum (ESI⁺): m/z = 512 [M+H]⁺

10

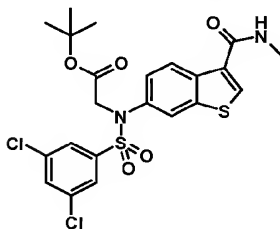
(39) tert. butyl [(3,5-dichloro-phenylsulphonyl)-(3-methylcarbamoyl-benzo[b]thiophen-5-yl)-amino]-acetate



Mass spectrum (ESI⁺): m/z = 546 [M+NH₄]⁺

15

(40) tert. butyl [(3,5-dichloro-phenylsulphonyl)-(3-methylcarbamoyl-benzo[b]thiophen-6-yl)-amino]-acetate

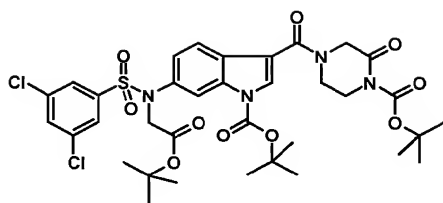


Mass spectrum (ESI⁺): m/z = 529 [M+H]⁺

20

(41) tert-butyl 6-[tert-butoxycarbonylmethyl-(3,5-dichloro-phenylsulphonyl)-amino]-3-(4-tert-butoxycarbonyl-3-oxo-piperazin-1-carbonyl)-indole-1-carboxylate

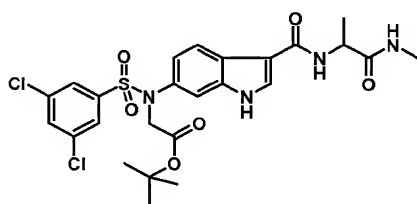
5



Mass spectrum (ESI⁺): m/z = 798 [M+NH₄]⁺

(42) tert. butyl {(3,5-dichloro-phenylsulphonyl)-[3-(1-methylcarbamoyl-ethylcarbamoyl)-1H-indol-6-yl]-amino}-acetate

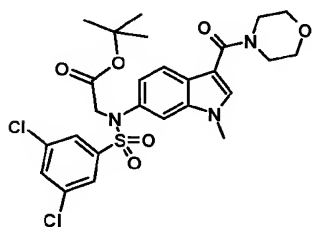
10



Mass spectrum (ESI⁻): m/z = 581 [M-H]⁻

(43) tert. butyl {(3,5-dichloro-phenylsulphonyl)-[1-methyl-3-(morpholine-4-carbonyl)-1H-indol-6-yl]-amino}-acetate

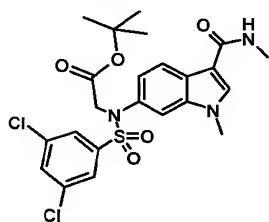
15



Mass spectrum (ESI⁻): m/z = 582 [M-H]⁻

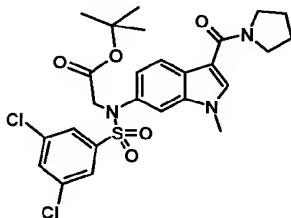
(44) tert. butyl [(3,5-dichloro-phenylsulphonyl)-(1-methyl-3-methylcarbamoyl-1H-indol-6-yl)-amino]-acetate

20



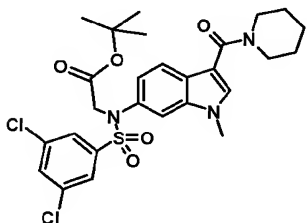
Mass spectrum (ESI⁺): m/z = 526 [M+H]⁺

- 5 (45) tert. butyl {(3,5-dichloro-phenylsulphonyl)-[1-methyl-3-(pyrrolidine-1-carbonyl)-1H-indol-6-yl]-amino}-acetate



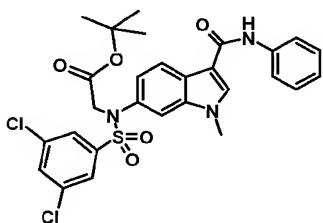
Mass spectrum (ESI⁺): m/z = 566 [M+H]⁺

- 10 (46) tert. butyl {(3,5-dichloro-phenylsulphonyl)-[1-methyl-3-(piperidine-1-carbonyl)-1H-indol-6-yl]-amino}-acetate



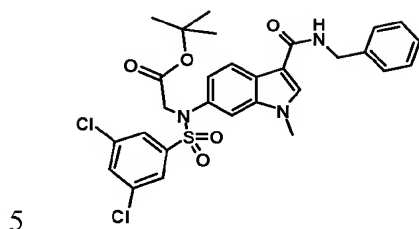
Mass spectrum (ESI⁺): m/z = 580 [M+H]⁺

- 15 (47) tert. butyl (3,5-dichloro-phenylsulphonyl)-(1-methyl-3-phenylcarbamoyl-1H-indol-6-yl)-amino]-acetate



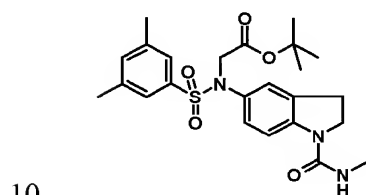
Mass spectrum (ESI⁺): m/z = 588 [M+H]⁺

- 20 (48) tert. butyl [(3-benzylcarbamoyl-1-methyl-1H-indol-6-yl)-(3,5-dichloro-phenylsulphonyl)-amino]-acetate



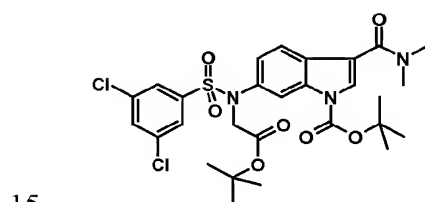
Mass spectrum (ESI⁺): m/z = 602 [M+H]⁺

(49) tert. butyl [(3,5-dimethyl-phenylsulphonyl)-(1-methylcarbamoyl-2,3-dihydro-1H-indol-5-yl)-amino]-acetate



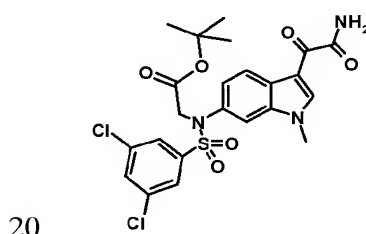
Mass spectrum (ESI⁺): m/z = 474 [M+H]⁺

(50) tert-butyl 6-[tert-butoxycarbonylmethyl-(3,5-dichloro-phenylsulphonyl)-amino]-3-dimethylcarbamoyl-indole-1-carboxylate



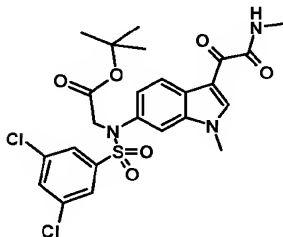
Mass spectrum (ESI⁺): m/z = 626 [M+H]⁺

(51) tert. butyl [(3-aminooxalyl-1-methyl-1H-indol-6-yl)-(3,5-dichloro-phenylsulphonyl)-amino]-acetate



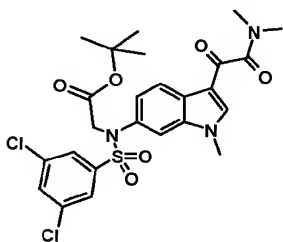
Mass spectrum (ESI⁺): m/z = 540 [M+H]⁺

- 5 (52) tert. butyl [(3,5-dichloro-phenylsulphonyl)-(1-methyl-3-methylaminooxalyl-1H-indol-6-yl)-amino]-acetate



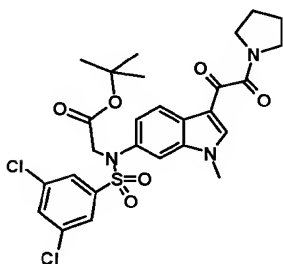
Mass spectrum (ESI⁺): m/z = 554 [M+H]⁺

- 10 (53) tert. butyl [(3,5-dichloro-phenylsulphonyl)-(3-dimethylaminooxalyl-1-methyl-1H-indol-6-yl)-amino]-acetate



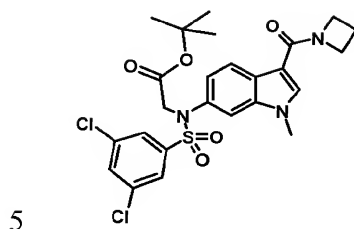
Mass spectrum (ESI⁺): m/z = 568 [M+H]⁺

- 15 (54) tert. butyl {(3,5-dichloro-phenylsulphonyl)-[1-methyl-3-(2-oxo-2-pyrrolidin-1-yl-acetyl)-1H-indol-6-yl]-amino}-acetate



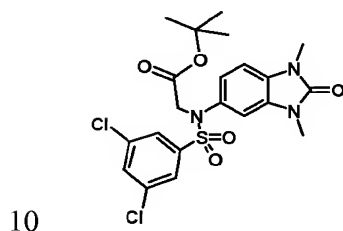
Mass spectrum (ESI⁺): m/z = 594 [M+H]⁺

- 20 (55) tert. butyl [(3-(azetidine-1-carbonyl)-1-methyl-1H-indol-6-yl)-(3,5-dichloro-phenylsulphonyl)-amino]-acetate



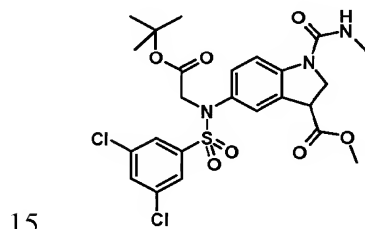
Mass spectrum (ESI⁺): m/z = 552 [M+H]⁺

(56) tert. butyl [(3,5-dichloro-phenylsulphonyl)-(1,3-dimethyl-2-oxo-2,3-dihydro-1H-benzimidazol-5-yl)-amino]-acetate



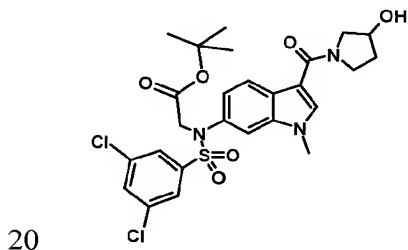
Mass spectrum (ESI⁺): m/z = 500 [M+H]⁺

(57) methyl 5-[tert-butoxycarbonylmethyl-(3,5-dichloro-phenylsulphonyl)-amino]-1-methylcarbamoyl-2,3-dihydro-1H-indole-3-carboxylate



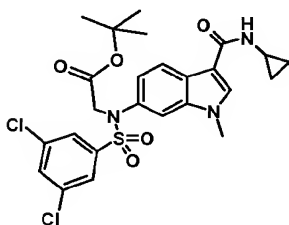
Mass spectrum (ESI⁺): m/z = 572 [M+H]⁺

(58) tert. butyl {(3,5-dichloro-phenylsulphonyl)-[3-(3-hydroxy-pyrrolidine-1-carbonyl)-1-methyl-1H-indol-6-yl]-amino}-acetate



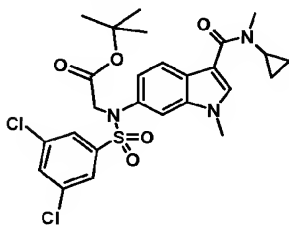
- 5 R_f value: 0.27 (silica gel: dichloromethane/methanol 9:1)

(59) tert. butyl [(3-cyclopropylcarbamoyl-1-methyl-1H-indol-6-yl)-(3,5-dichloro-phenylsulphonyl)-amino]-acetate



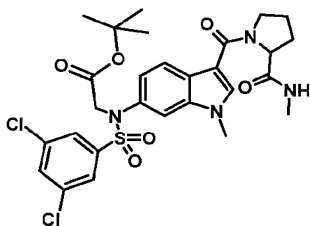
- 10 R_f value: 0.39 (silica gel: petroleum ether/ethyl acetate 1:2)

(60) tert. butyl [[3-(cyclopropyl-methyl-carbamoyl)-1-methyl-1H-indol-6-yl]-(3,5-dichloro-phenylsulphonyl)-amino]-acetate



- 15 R_f value: 0.34 (silica gel: petroleum ether/ethyl acetate 1:2)

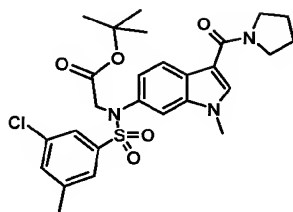
(61) tert. butyl {(3,5-dichloro-phenylsulphonyl)-[1-methyl-3-(2-methylcarbamoyl-pyrrolidine-1-carbonyl)-1H-indol-6-yl]-amino}-acetate



- 20 R_f value: 0.44 (silica gel: dichloromethane/methanol 9:1)

(62) tert. butyl {(3-chloro-5-methyl-phenylsulphonyl)-[1-methyl-3-(pyrrolidine-1-carbonyl)-1H-indol-6-yl]-amino}-acetate

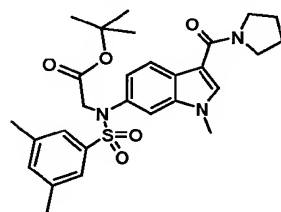
5



Mass spectrum (ESI⁺): m/z = 546 [M+H]⁺

(63) tert. butyl {(3,5-dimethyl-phenylsulphonyl)-[1-methyl-3-(pyrrolidine-1-carbonyl)-1H-indol-6-yl]-amino}-acetate

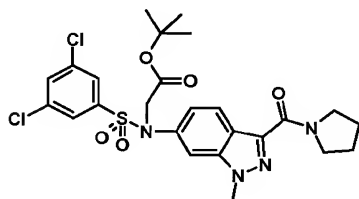
10



Mass spectrum (ESI⁺): m/z = 526 [M+H]⁺

(64) tert. butyl {(3,5-dichloro-phenylsulphonyl)-[1-methyl-3-(pyrrolidine-1-carbonyl)-1H-indazol-6-yl]-amino}-acetate

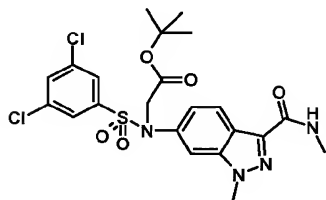
15



Mass spectrum (ESI⁺): m/z = 567 [M+H]⁺

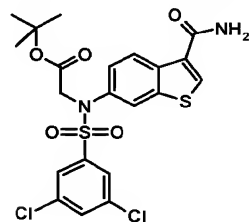
(65) tert. butyl [(3,5-dichloro-phenylsulphonyl)-(1-methyl-3-methylcarbamoyl-1H-indazol-6-yl)-amino]-acetate

20



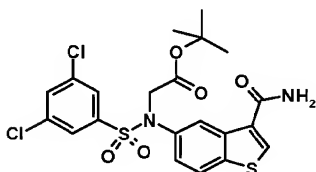
Mass spectrum (ESI⁺): m/z = 527 [M+H]⁺

- 5 (66) tert. butyl [(3-carbamoyl-benzo[b]thiophen-6-yl)-(3,5-dichloro-phenylsulphonyl)-amino]-acetate



Mass spectrum (ESI⁺): m/z = 532 [M+NH₄]⁺

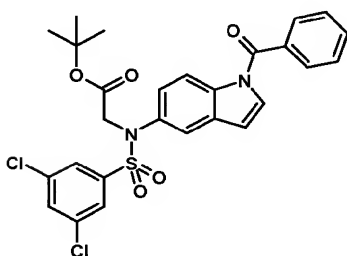
- 10 (67) tert. butyl [(3-carbamoyl-benzo[b]thiophen-5-yl)-(3,5-dichloro-phenylsulphonyl)-amino]-acetate



Mass spectrum (ESI⁺): m/z = 532 [M+NH₄]⁺

15

Example VII



tert. butyl [(1-benzoyl-1H-indol-5-yl)-(3,5-dichloro-phenylsulphonyl)-amino]-
acetate

20

50 mg tert. butyl [(3,5-dichloro-phenylsulphonyl)-(1H-indol-5-yl)-amino]-
 acetate are dissolved in 2 ml dichloromethane. 5 mg powdered sodium
 hydroxide and 19 µl benzoyl chloride are added. Then the mixture is stirred
 for 4 hours at ambient temperature, divided between 1 N sodium hydroxide
 25 solution and ethyl acetate, the aqueous phase is extracted with ethyl acetate

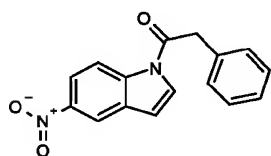
- 5 and the combined organic phases are dried with magnesium sulphate. The solvents are eliminated in vacuo and the residue is chromatographed on silica gel (cyclohexane/ethyl acetate 10:1 to 1:2).

Yield: 15 mg (24 % of theory)

Mass spectrum (ESI⁺): m/z = 576 [M+NH₄]⁺

10

Example VIII



15 1-(5-nitro-indol-1-yl)-2-phenyl-ethanone

300 mg 5-nitroindole are dissolved in 10 ml of tetrahydrofuran. 81 mg sodium hydride (60 % in mineral oil) are added and the mixture is stirred for 1 hour at ambient temperature. Then 294 µl phenylacetic acid chloride are added dropwise and the mixture is stirred for another 3 hours. It is divided between

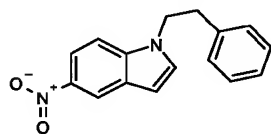
- 20 saturated ammonium chloride solution and ethyl acetate. The aqueous phase is extracted with ethyl acetate and the combined organic phases are dried on magnesium sulphate. The solvents are eliminated in vacuo and the residue is chromatographed on silica gel (cyclohexane/ethyl acetate 10:1 to 1:3).

Yield: 250 mg (48 % of theory)

- 25 Mass spectrum (ESI⁺): m/z = 281 [M+H]⁺

The following compounds are obtained analogously to Example VIII:

(1) 5-nitro-1-(phenylethyl)-1H-indole

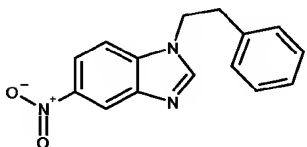


30

Dimethylformamide is used instead of tetrahydrofuran.

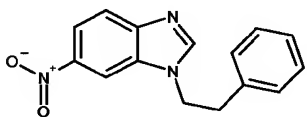
- 5 Mass spectrum (ESI⁺): m/z = 267 [M+H]⁺

(2) 5-nitro-1-(phenylethyl)-1H-benzimidazole



and

- 10 6-nitro-1-(phenylethyl)-1H-benzimidazole



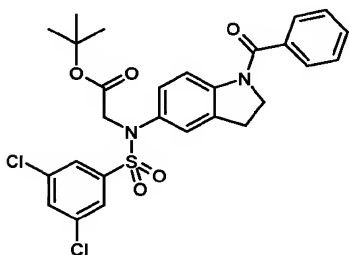
Dimethylformamide is used instead of tetrahydrofuran.

The compounds are obtained as a mixture of regioisomers.

Mass spectrum (ESI⁺): m/z = 268 [M+H]⁺

15

Example IX



tert. butyl [(1-benzoyl-2,3-dihydro-1H-indol-5-yl)-(3,5-dichloro-phenylsulphonyl)-amino]-acetate

20

150 mg tert. butyl [(3,5-dichloro-phenylsulphonyl)-(2,3-dihydro-1H-indol-5-yl)-amino]-acetate are dissolved in 5 ml dichloromethane. 110 mg potassium carbonate and 45 µl benzoyl chloride are added, the mixture is stirred for 3 hours at ambient temperature and then divided between dichloromethane and water. The organic phase is washed with water and then dried on magnesium sulphate. The solvents are eliminated in vacuo.

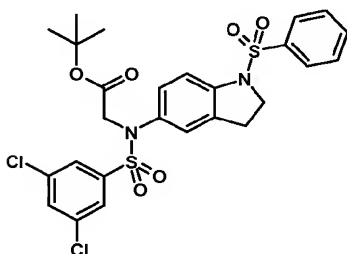
25

Yield: 170 mg (92 % of theory)

- 5 Mass spectrum (ESI⁺): m/z = 561 [M+H]⁺

The following compounds are obtained analogously to Example IX:

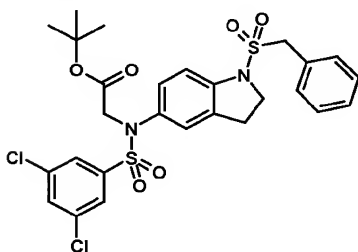
- (1) tert. butyl [(1-phenylsulphonyl-2,3-dihydro-1H-indol-5-yl)-(3,5-dichloro-phenylsulphonyl)-amino]-acetate
- 10



Phenylsulphonyl chloride is used instead of benzoyl chloride.

Mass spectrum (ESI⁺): m/z = 614 [M+NH₄]⁺

- (2) tert. butyl [(3,5-dichloro-phenylsulphonyl)-(1-phenylmethanesulphonyl-2,3-dihydro-1H-indol-5-yl)-amino]-acetate
- 15

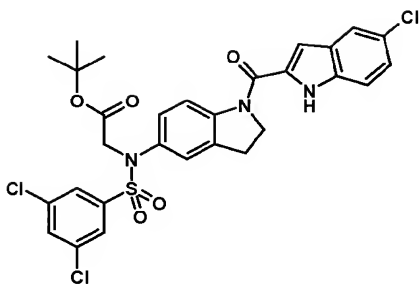


Phenylmethanesulphonyl chloride is used instead of benzoyl chloride.

Mass spectrum (ESI⁺): m/z = 628 [M+NH₄]⁺

20

Example X

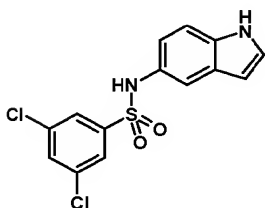


5

tert. butyl [(1-(5-chloro-1H-indol-2-carbonyl)-2,3-dihydro-1H-indol-5-yl)-(3,5-dichloro-phenylsulphonyl)-amino]-acetate

- 55 mg 5-chloro-1H-indol-2-carboxylic acid are dissolved in 2 ml of thionyl chloride and heated to 80°C for 1 hour. The solvent is eliminated in vacuo and the residue is twice combined with dichloromethane and the latter is eliminated again in vacuo. The residue is taken up in 5 ml dichloromethane and the solution is added dropwise to a mixture of 100 mg tert. butyl [(3,5-dichloro-phenylsulphonyl)-(2,3-dihydro-1H-indol-5-yl)-amino]-acetate and 60 mg potassium carbonate in 2 ml dimethylformamide. The mixture is stirred for 2 hours at ambient temperature, diluted with ethyl acetate and washed with 1 N HCl and saturated sodium chloride solution. After drying with magnesium sulphate the solvents are eliminated in vacuo and the residue is chromatographed on silica gel (cyclohexane/ethyl acetate 10:1 to 1:2). Yield: 60 mg (43 % of theory)
- Mass spectrum (ESI⁺): m/z = 634 [M+H]⁺

Example XI



3,5-dichloro-N-(1H-indol-5-yl)-phenylsulphonamide

100 mg 5-aminoindole are dissolved in 10 ml of pyridine. 186 mg 3,5-dichlorophenylsulphonyl chloride are added thereto and the mixture is stirred for 4 hours at ambient temperature. The solvent is eliminated in vacuo and

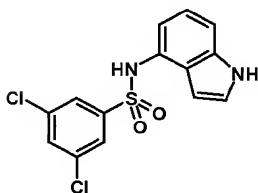
5 the residue is divided between water and ethyl acetate. The aqueous phase is extracted with ethyl acetate and the combined organic phases are washed with saturated sodium chloride solution. After drying with magnesium sulphate the solvents are eliminated in vacuo and the residue is chromatographed on silica gel (cyclohexane/ethyl acetate 10:1 to 1:5).

10 Yield: 240 mg (93 % of theory)

Mass spectrum (ESI⁺): m/z = 341 [M+H]⁺

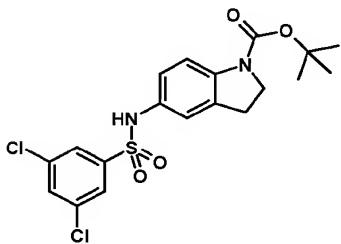
The following compounds are obtained analogously to Example XI:

15 (1) 3,5-dichloro-N-(1H-indol-4-yl)-phenylsulphonamide



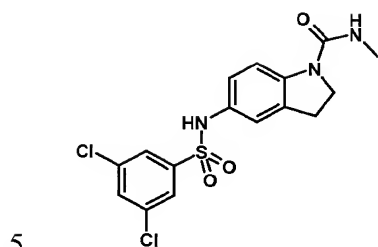
Mass spectrum (ESI⁺): m/z = 341 [M+H]⁺

20 (2) tert-butyl 5-(3,5-dichloro-phenylsulphonylamino)-2,3-dihydro-indole-1-carboxylate



Mass spectrum (ESI⁺): m/z = 460 [M+NH₄]⁺

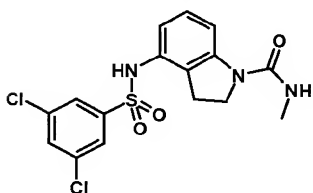
25 (3) 5-(3,5-dichloro-phenylsulphonylamino)-2,3-dihydro-indole-1-carboxylic acid-methylamide



The crude product is extracted from diisopropylether.

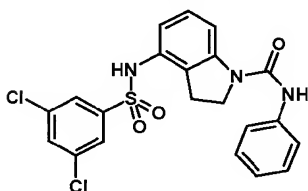
Mass spectrum (ESI⁺): m/z = 400 [M+H]⁺

- 10 (4) 4-(3,5-dichloro-phenylsulphonylamino)-2,3-dihydro-indole-1-carboxylic acid-methylamide



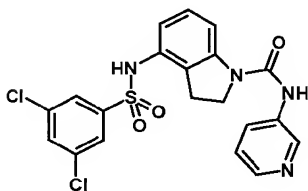
Mass spectrum (ESI⁺): m/z = 400 [M+H]⁺

- 15 (5) 4-(3,5-dichloro-phenylsulphonylamino)-2,3-dihydro-indole-1-carboxylic acid-phenylamide



Mass spectrum (ESI⁺): m/z = 462 [M+H]⁺

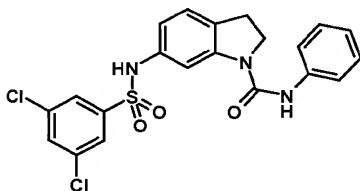
- 20 (6) 4-(3,5-dichloro-phenylsulphonylamino)-2,3-dihydro-indole-1-carboxylic acid-pyridin-3-ylamide



Mass spectrum (ESI⁺): m/z = 463 [M+H]⁺

5

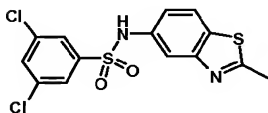
(7) 3,5-dichloro-N-[4-ethyl-3-(1-methyl-3-phenyl-ureido)-phenyl]-phenylsulphonamide



10 The reaction is carried out in dichloromethane/pyridine 2:1. The crude product is extracted from diisopropylether.

Mass spectrum (ESI⁺): m/z = 462 [M+H]⁺

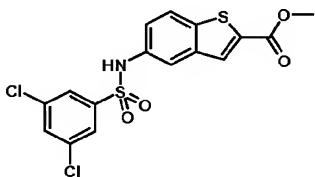
(8) 3,5-dichloro-N-(2-methyl-benzothiazole-5-yl)-phenylsulphonamide



15 The reaction is carried out in dichloromethane with 2 equivalents of triethylamine.

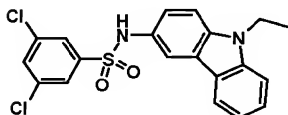
Mass spectrum (ESI⁺): m/z = 373 [M+H]⁺

20 (9) methyl 5-(3,5-dichloro-phenylsulphonylamino)-benzo[b]thiophen-2-carboxylate



Mass spectrum (ESI⁻): m/z = 414 [M-H]⁻

(10) 3,5-dichloro-N-(9-ethyl-9H-carbazol-3-yl)-phenylsulphonamide

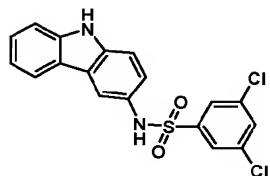


25

The reaction is carried out in dichloromethane/pyridine 5:1.

- 5 The product is further reacted directly in Example VI (24).

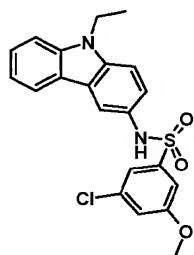
(11) N-(9H-carbazol-3-yl)-3,5-dichloro-phenylsulphonamide



The reaction is carried out in dichloromethane/pyridine 5:1.

- 10 Mass spectrum (ESI⁺): m/z = 389 [M+H]⁺

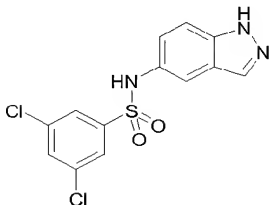
(12) 3-chloro-N-(9-ethyl-9H-carbazol-3-yl)-5-methoxy-phenylsulphonamide



Mass spectrum (ESI⁺): m/z = 415 [M+H]⁺

15

(13) 3,5-dichloro-N-(1H-indazol-5-yl)-phenylsulphonamide



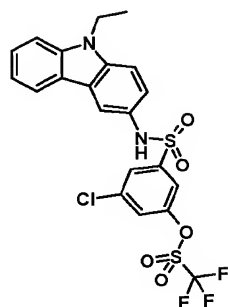
The product additionally contains 3,5-dichloro-N-[1-(3,5-dichloro-phenylsulphonyl)-3-methyl-1H-indazol-5-yl]-phenylsulphonamide.

- 20 Mass spectrum (ESI⁻): m/z = 340 [M-H]⁻

R_f value: 0.60 (silica gel: ethyl acetate/petroleum ether 2:1)

(14) 3-chloro-N-(9-ethyl-9H-carbazol-3-yl)-5-trifluoromethylsulphonyloxy-phenylsulphonamide

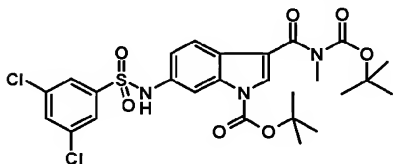
5



Mass spectrum (ESI^+): $m/z = 533$ $[\text{M}+\text{H}]^+$

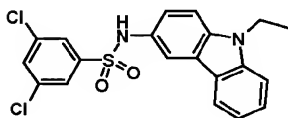
(15) tert-butyl 3-(tert-butoxycarbonyl-methyl-aminocarbonyl)-6-(3,5-dichlorophenylsulphonylamino)-indole-1-carboxylate

10



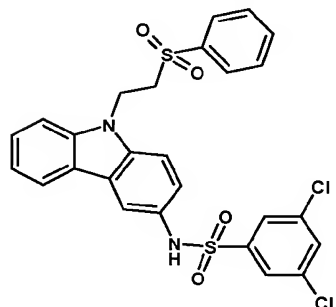
R_f value: 0.63 (silica gel: petroleum ether/ethyl acetate 2:1)

(16) 3,5-dichloro-N-(9-ethyl-9H-carbazol-3-yl)-phenylsulphonamide



15 Mass spectrum (ESI^+): $m/z = 533$ $[\text{M}+\text{H}]^+$

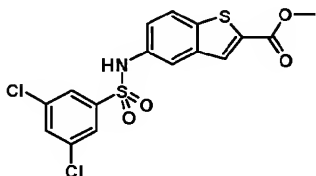
(17) N-[9-(2-phenylsulphonyl-ethyl)-9H-carbazol-3-yl]-3,5-dichlorophenylsulphonamide



20 Mass spectrum (ESI^+): $m/z = 576$ $[\text{M}+\text{NH}_4]^+$

5

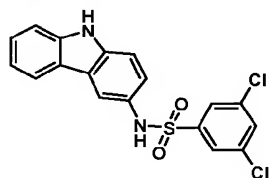
(18) methyl 5-(3,5-dichloro-phenylsulphonylamino)-benzo[b]thiophen-2-carboxylate



Mass spectrum (ESI⁺): m/z = 433 [M+NH₄]⁺

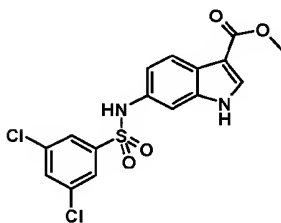
10

(19) N-(9H-carbazol-3-yl)-3,5-dichloro-phenylsulphonamide



Mass spectrum (ESI⁻): m/z = 389 [M-H]⁻

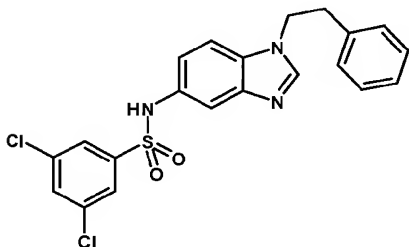
15 (20) methyl 6-(3,5-dichloro-phenylsulphonylamino)-1H-indole-3-carboxylate



Mass spectrum (ESI⁺): m/z = 399 [M+H]⁺

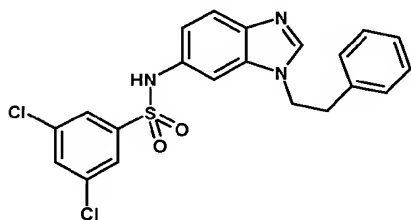
(21) 3,5-dichloro-N-[1-(phenylethyl)-1H-benzimidazol-5-yl]-phenylsulphonamide

20



and

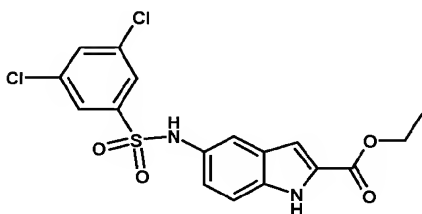
- 5 3,5-dichloro-N-[3-(phenylethyl)-3H-benzimidazol-5-yl]-phenylsulphonamide



are obtained as a mixture and used as such in VI (29).

Mass spectrum (ESI⁺): m/z = 446 [M+H]⁺

- 10 (22) ethyl 5-(3,5-dichloro-phenylsulphonylamino)-1H-indole-2-carboxylate

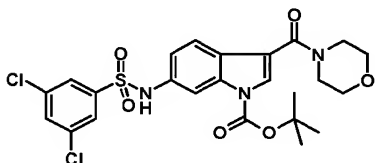


The reaction is carried out in dichloromethane. 1.4 equivalents 2,6-lutidine are used as the base.

Mass spectrum (ESI⁻): m/z = 411 [M-H]⁻

15

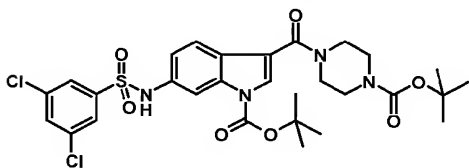
- (23) tert-butyl 6-(3,5-dichloro-phenylsulphonylamino)-3-(morpholine-4-carbonyl)-indole-1-carboxylate



R_f value: 0.41 (silica gel: petroleum ether/ethyl acetate 1:1)

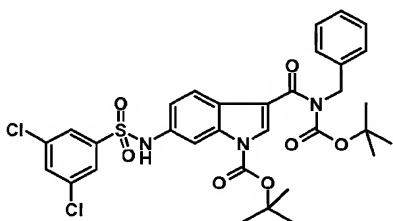
20

- (24) tert-butyl 3-(4-tert-butoxycarbonyl-piperazin-1-carbonyl)-6-(3,5-dichloro-phenylsulphonylamino)-indole-1-carboxylate



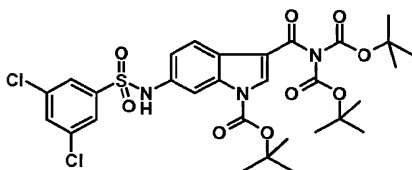
- 5 R_f value: 0.63 (silica gel: petroleum ether/ethyl acetate 1:1)

(25) tert-butyl 3-(benzyl-tert-butoxycarbonyl-aminocarbonyl)-6-(3,5-dichloro-phenylsulphonylamino)-indole-1-carboxylate



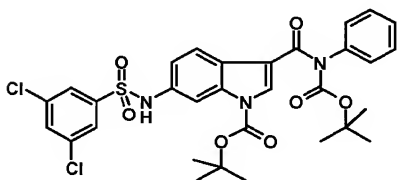
- 10 R_f value: 0.65 (silica gel: petroleum ether/ethyl acetate 2:1)

(26) tert-butyl 3-(bis-tert.-butoxycarbonyl)-aminocarbonyl-6-(3,5-dichloro-phenylsulphonylamino)-indole-1-carboxylate



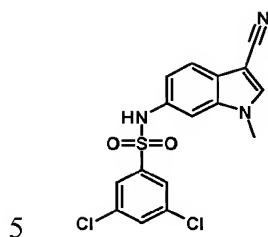
- 15 R_f value: 0.67 (silica gel: petroleum ether/ethyl acetate 2:1)

(27) tert-butyl 3-(tert-butoxycarbonyl-phenyl-aminocarbonyl)-6-(3,5-dichloro-phenylsulphonylamino)-indole-1-carboxylate



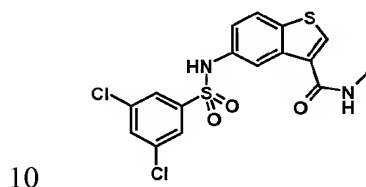
- 20 R_f value: 0.74 (silica gel: petroleum ether/ethyl acetate 2:1)

(28) 3,5-dichloro-N-(3-cyano-1-methyl-1H-indol-6-yl)-phenylsulphonamide



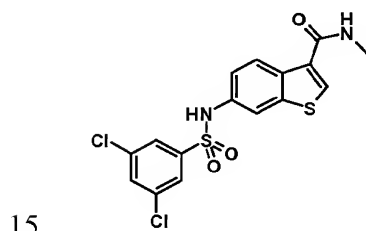
Mass spectrum (ESI⁻): m/z = 378 [M-H]⁻

(29) 5-(3,5-dichloro-phenylsulphonylamino)-benzo[b]thiophen-3-carboxylic acid-methylamide



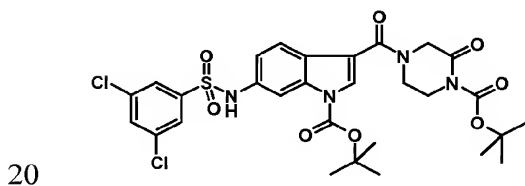
Mass spectrum (ESI⁻): m/z = 413 [M-H]⁻

(30) 6-(3,5-dichloro-phenylsulphonylamino)-benzo[b]thiophen-3-carboxylic acid-methylamide



Mass spectrum (ESI⁺): m/z = 415 [M+H]⁺

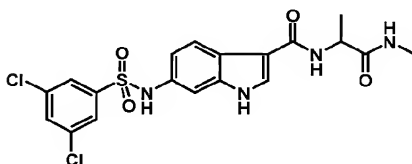
(31) tert-butyl 3-(4-tert-butoxycarbonyl-3-oxo-piperazin-1-carbonyl)-6-(3,5-dichloro-phenylsulphonylamino)-indole-1-carboxylate



R_f value: 0.73 (silica gel: petroleum ether/ethyl acetate 1:1)

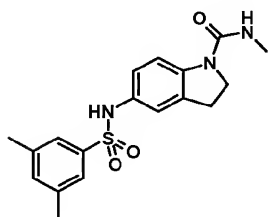
(32) 6-(3,5-dichloro-phenylsulphonylamino)-1H-indole-3-carboxylic acid-(1-

5 methylcarbamoyl-ethyl)-amide



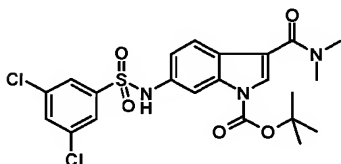
R_f value: 0.35 (silica gel: dichloromethane/methanol 9:1)

10 (33) 5-(3,5-dimethyl-phenylsulphonylamino)-2,3-dihydro-indole-1-carboxylic acid-methylamide



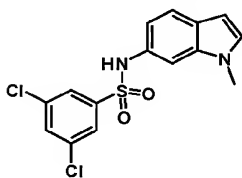
Mass spectrum (ESI⁺): m/z = 360 [M+H]⁺

15 (34) tert-butyl 6-(3,5-dichloro-phenylsulphonylamino)-3-dimethylcarbamoyl-indole-1-carboxylate



R_f value: 0.60 (silica gel: petroleum ether/ethyl acetate 1:2)

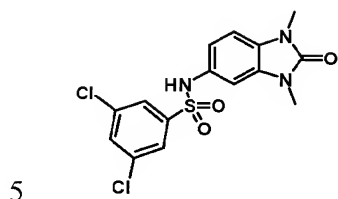
(35) 3,5-dichloro-N-(1-methyl-1H-indol-6-yl)-phenylsulphonamide



20

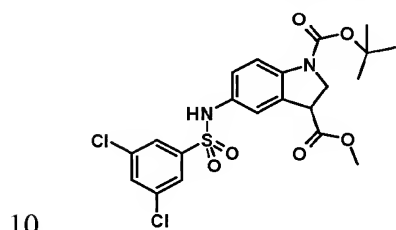
Mass spectrum (ESI⁺): m/z = 355 [M+H]⁺

(36) 3,5-dichloro-N-(1,3-dimethyl-2-oxo-2,3-dihydro-1H-benzimidazol-5-yl)-phenylsulphonamide



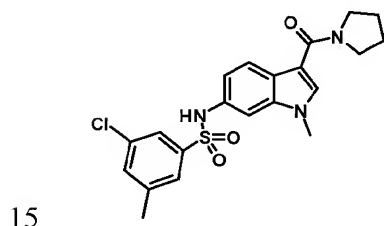
Mass spectrum (ESI⁺): m/z = 386 [M+H]⁺

(37) 1-tert-butyl-3-methyl 5-(3,5-dichloro-phenylsulphonylamino)-2,3-dihydro-indole-1,3-dicarboxylate



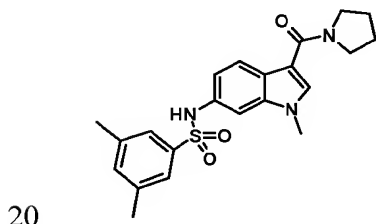
R_f value: 0.30 (silica gel: petroleum ether/ethyl acetate 3:1)

(38) 3-chloro-5-methyl-N-[1-methyl-3-(pyrrolidine-1-carbonyl)-1H-indol-6-yl]-phenylsulphonamide



Mass spectrum (ESI⁺): m/z = 432 [M+H]⁺

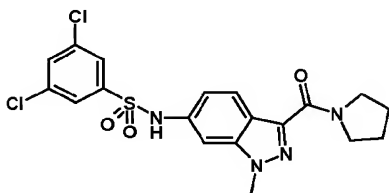
(39) 3,5-dimethyl-N-[1-methyl-3-(pyrrolidine-1-carbonyl)-1H-indol-6-yl]-phenylsulphonamide



Mass spectrum (ESI⁺): m/z = 412 [M+H]⁺

5

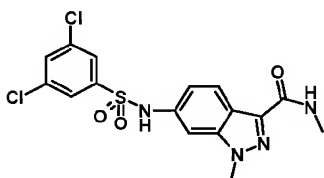
(40) 3,5-dichloro-N-[1-methyl-3-(pyrrolidine-1-carbonyl)-1H-indazol-6-yl]-phenylsulphonamide



Mass spectrum (ESI⁺): m/z = 453 [M+H]⁺

10

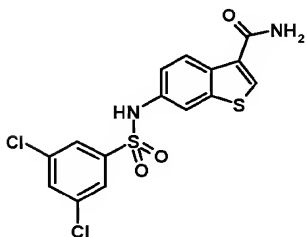
(41) 6-(3,5-dichloro-phenylsulphonylamino)-1-methyl-1H-indazol-3-carboxylic acid-methylamide



Mass spectrum (ESI⁺): m/z = 413 [M+H]⁺

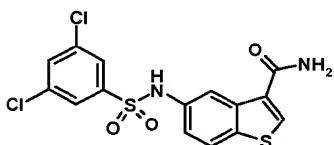
15

(42) 6-(3,5-dichloro-phenylsulphonylamino)-benzo[b]thiophen-3-carboxylic acid-amide



and

20 5-(3,5-dichloro-phenylsulphonylamino)-benzo[b]thiophen-3-carboxylic acid-amide

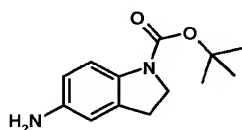


Obtained from the reaction of a mixture of 6-amino-benzo[b]thiophene-3-carboxylic acid-amide and 5-amino-benzo[b]thiophene-3-carboxylic acid-

- 5 amide (Example XII (30)). The crude product is dissolved in hot ethyl acetate. After cooling to ambient temperature the precipitated solid (5-(3,5-dichloro-phenylsulphonylamino)-benzo[b]thiophene-3-carboxylic acid-amide) is filtered off. The mother liquor is freed from the solvents in vacuo and the residue is chromatographed on silica gel, to obtain 6-(3,5-dichloro-phenylsulphonylamino)-benzo[b]thiophene-3-carboxylic acid-amide.
- 10 Mass spectrum (ESI⁺): m/z = 401 [M+H]⁺
- 6-(3,5-dichloro-phenylsulphonylamino)-benzo[b]thiophene-3-carboxylic acid-amide and 5-(3,5-dichloro-phenylsulphonylamino)-benzo[b]thiophene-3-carboxylic acid-amide

15

Example XII

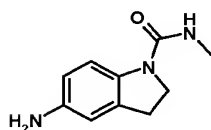


tert-butyl 5-amino-2,3-dihydro-indole-1-carboxylate

- 20 6.8 g tert-butyl 5-nitro-indole-1-carboxylate are dissolved in 120 ml of methanol. 600 mg palladium on charcoal (10%) are added thereto and the mixture is hydrogenated for 1.5 hours at ambient temperature. Then the catalyst is filtered off and the solvent is eliminated in vacuo.
- Yield: 6 g (100 % of theory)
- 25 Mass spectrum (ESI⁺): m/z = 235 [M+H]⁺

The following compounds are obtained analogously to Example XII:

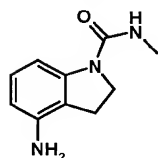
(1) 5-amino-2,3-dihydro-indole-1-carboxylic acid-methylamide



30

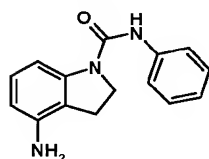
Mass spectrum (ESI⁺): m/z = 192 [M+H]⁺

- 5 (2) 4-amino-2,3-dihydro-indole-1-carboxylic acid-methylamide



Mass spectrum (ESI⁺): m/z = 192 [M+H]⁺

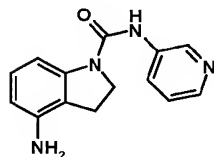
- (3) 4-amino-2,3-dihydro-indole-1-carboxylic acid-phenylamide



10

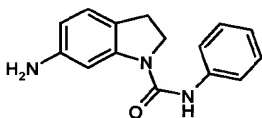
Mass spectrum (ESI⁺): m/z = 254 [M+H]⁺

- (4) 4-amino-2,3-dihydro-indole-1-carboxylic acid-pyridin-3-ylamide



- 15 Mass spectrum (ESI⁺): m/z = 255 [M+H]⁺

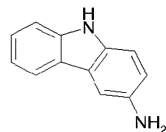
- (5) 1-(5-amino-2-ethyl-phenyl)-1-methyl-3-phenyl-urea



The crude product is extracted from diisopropylether.

- 20 Mass spectrum (ESI⁺): m/z = 254 [M+H]⁺

- (6) 9H-carbazol-3-ylamine

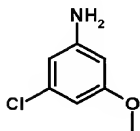


Tetrahydrofuran is used as solvent.

- 25 Mass spectrum (ESI⁺): m/z = 183 [M+H]⁺

5

(7) 1-chloro-3-methoxy-5-amino-benzene

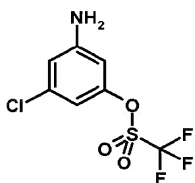


Tetrahydrofuran is used as solvent.

Mass spectrum (ESI⁺): m/z = 158 [M+H]⁺

10

(8) 3-amino-5-chloro-phenyl trifluoromethanesulphonate

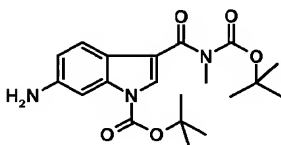


Tetrahydrofuran is used as solvent.

The product is further reacted directly in XVII (2).

15

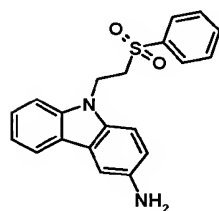
(9) tert-butyl 6-amino-3-(tert-butoxycarbonyl-methyl-aminocarbonyl)-indole-1-carboxylate



Tetrahydrofuran is used as solvent.

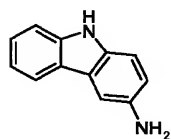
20 R_f value: 0.42 (silica gel: petroleum ether/ethyl acetate 2:1)

(10) 9-(2-phenylsulphonyl-ethyl)-9H-carbazol-3-ylamine

Mass spectrum (ESI⁺): m/z = 351 [M+H]⁺

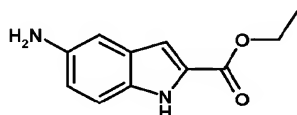
25

5 (11) 9H-carbazol-3-ylamine



Mass spectrum (ESI⁺): m/z = 183 [M+H]⁺

(12) ethyl 5-amino-1H-indole-2-carboxylate

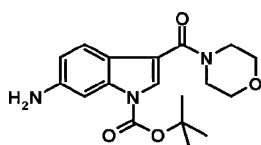


10

A 3:2:2 mixture of ethyl acetate, methanol and tetrahydrofuran is used as solvent.

Mass spectrum (ESI⁺): m/z = 205 [M+H]⁺

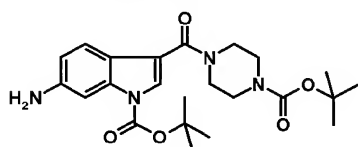
15 (13) tert-butyl 6-amino-3-(morpholine-4-carbonyl)-indole-1-carboxylate



Tetrahydrofuran is used as solvent.

R_f value: 0.21 (silica gel: petroleum ether/ethyl acetate 1:1)

20 (14) tert-butyl 6-amino-3-(4-tert-butoxycarbonyl-piperazin-1-carbonyl)-indole-1-carboxylate



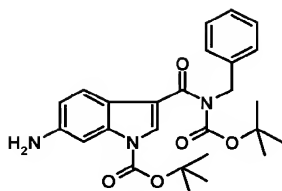
Tetrahydrofuran is used as solvent.

R_f value: 0.33 (silica gel: petroleum ether/ethyl acetate 1:1)

25

(15) tert-butyl 6-amino-3-(benzyl-tert-butoxycarbonyl-aminocarbonyl)-indole-1-carboxylate

5

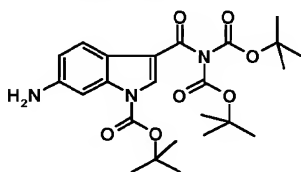


Tetrahydrofuran is used as solvent.

R_f value: 0.44 (silica gel: petroleum ether/ethyl acetate 2:1)

10

(16) tert-butyl 6-amino-3-(bis-tert-butoxycarbonyl)-aminocarbonyl-indole-1-carboxylate

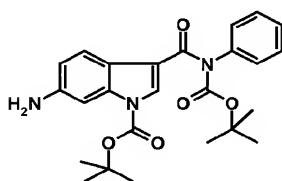


Tetrahydrofuran is used as solvent.

R_f value: 0.62 (silica gel: petroleum ether/ethyl acetate 2:1)

15

(17) tert-butyl 6-amino-3-(tert-butoxycarbonyl-phenyl-aminocarbonyl)-indole-1-carboxylate

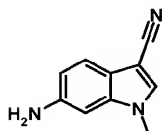


Tetrahydrofuran is used as solvent.

R_f value: 0.45 (silica gel: petroleum ether/ethyl acetate 2:1)

20

(18) 6-amino-1-methyl-1H-indole-3-carbonitrile

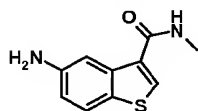


The crude product is crystallised from isopropanol.

Mass spectrum (ESI⁺): m/z = 172 [M+H]⁺

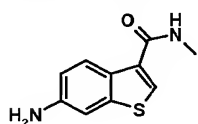
25

- 5 (19) 5-amino-benzo[b]thiophene-3-carboxylic acid-methylamide



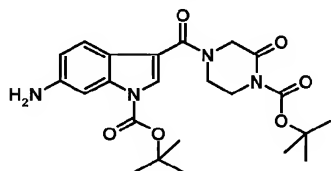
Tetrahydrofuran/methanol 2:1 is used as solvent. The crude product is further reacted directly in XI (29).

- 10 (20) 6-amino-benzo[b]thiophene-3-carboxylic acid-methylamide



Tetrahydrofuran/methanol 2:1 is used as solvent. The crude product is further reacted directly in XI (30).

- 15 (21) tert-butyl 6-amino-3-(4-tert-butoxycarbonyl-3-oxo-piperazin-1-carbonyl)-indole-1-carboxylate

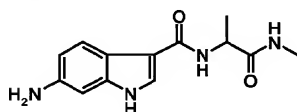


Tetrahydrofuran is used as solvent.

R_f value: 0.54 (silica gel: petroleum ether/ethyl acetate 1:1)

20

- (22) 6-amino-1H-indole-3-carboxylic acid-(1-methylcarbamoyl-ethyl)-amide



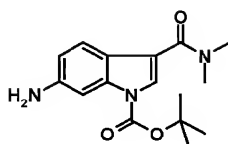
Tetrahydrofuran is used as solvent.

R_f value: 0.46 (silica gel: dichloromethane/methanol 5:1)

25

- (23) tert-butyl 6-amino-3-dimethylcarbamoyl-indole-1-carboxylate

5

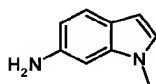


Tetrahydrofuran is used as solvent.

R_f value: 0.32 (silica gel: petroleum ether/ethyl acetate 1:2)

(24) 1-methyl-1H-indol-6-ylamine

10

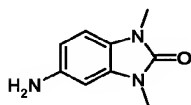


Tetrahydrofuran is used as solvent.

Mass spectrum (ESI⁺): $m/z = 147$ [M+H]⁺

(25) 5-amino-1,3-dimethyl-1,3-dihydro-benzimidazol-2-one

15

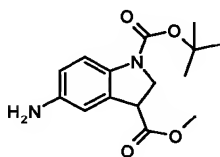


Tetrahydrofuran is used as solvent.

Mass spectrum (ESI⁺): $m/z = 178$ [M+H]⁺

(26) 1-tert-butyl-3-methyl 5-amino-2,3-dihydro-indole-1,3-dicarboxylate

20

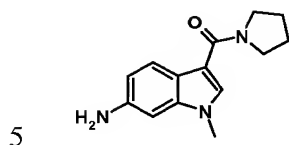


Obtained from the hydrogenation of 1-tert-butyl-3-methyl 5-nitro-indole-1,3-dicarboxylate in ethyl acetate/methanol/tetrahydrofuran 10:7:7. It is hydrogenated at 50°C and 15 bar.

R_f value: 0.30 (silica gel: petroleum ether/ethyl acetate 1:1)

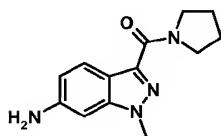
25

(27) (6-amino-1-methyl-1H-indol-3-yl)-pyrrolidin-1-yl-methanone



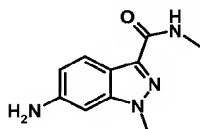
Mass spectrum (ESI⁺): m/z = 244 [M+H]⁺

(28) (6-amino-1-methyl-1H-indazol-3-yl)-pyrrolidin-1-yl-methanone



10 R_f value: 0.40 (silica gel: dichloromethane/methanol 95:5)

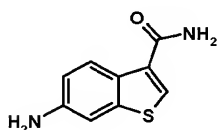
(29) 6-amino-1-methyl-1H-indazol-3-carboxylic acid-methylamide



R_f value: 0.40 (silica gel: dichloromethane/methanol 95:5)

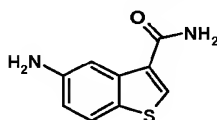
15

(30) 6-amino-benzo[b]thiophene-3-carboxylic acid-amide



and

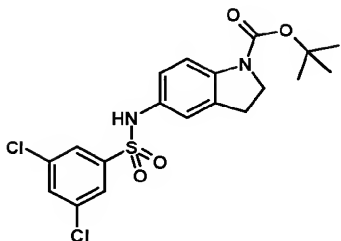
5-amino-benzo[b]thiophene-3-carboxylic acid-amide



20

Obtained as a mixture from the reaction of a mixture of 6-nitro-benzo[b]thiophene-3-carboxylic acid-amide and 5-nitro-benzo[b]thiophene-3-carboxylic acid-amide (Example IXXX (9)). The crude product is further reacted directly in Example XI (42).

25

5 Example XIII

tert-butyl 5-(3,5-dichloro-phenylsulphonylamino)-2,3-dihydro-indole-1-carboxylate

- 10 6.6 g tert-butyl 5-nitro-2,3-dihydro-indole-1-carboxylate are dissolved in 120 ml of methanol. 600 mg palladium on charcoal (10%) are added and the mixture is hydrogenated until no more educt can be detected by thin layer chromatography. The catalyst is suction filtered and washed with methanol. The solvent is eliminated in vacuo and the residue is taken up in 30 ml of
- 15 pyridine. 6.1 g of 3,5-dichlorophenylsulphonyl chloride are added and the mixture is stirred for 5 hours at ambient temperature. Then the pyridine is eliminated in vacuo and the residue is divided between 1 N HCl and ethyl acetate. The organic phase is washed with saturated sodium hydrogen carbonate solution and with saturated sodium chloride solution. After drying
- 20 with magnesium sulphate the solvent is eliminated in vacuo.

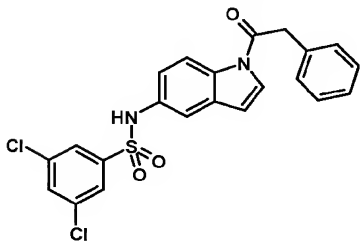
Yield: 11 g (99 % of theory)

Mass spectrum (ESI⁻): m/z = 441 [M-H]⁻

The following compounds are obtained analogously to Example XIII:

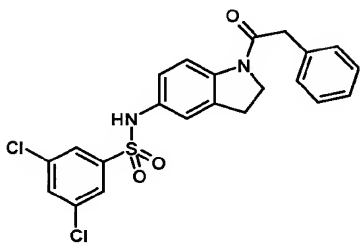
25

(1) 3,5-dichloro-N-(1-phenylacetyl-1H-indol-5-yl)-phenylsulphonamide



and 3,5-dichloro-N-(1-phenylacetyl-2,3-dihydro-1H-indol-5-yl)-

5 phenylsulphonamide

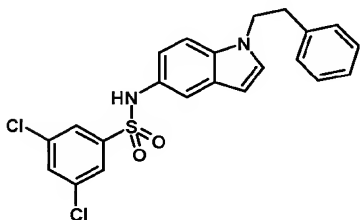


The hydrogenation is carried out in the presence of 1.2 equivalents of 1 N HCl. The crude product is chromatographed on silica gel.

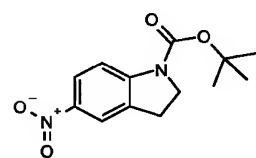
Mass spectrum (ESI⁻): m/z = 457 [M-H]⁻ (3,5-dichloro-N-(1-phenylacetyl-1H-indol-5-yl)-phenylsulphonamide)

Mass spectrum (ESI⁻): m/z = 459 [M-H]⁻ (3,5-dichloro-N-(1-phenylacetyl-2,3-dihydro-1H-indol-5-yl)-phenylsulphonamide)

(2) 3,5-dichloro-N-[1-(phenylethyl)-1H-indol-5-yl]-phenylsulphonamide



Mass spectrum (ESI⁺): m/z = 445 [M+H]⁺

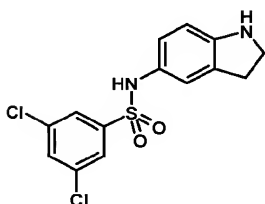
Example XIVtert-butyl 5-nitro-2,3-dihydro-indole-1-carboxylate

5 g 5-nitro-2,3-dihydro-1H-indole are dissolved in 70 ml acetonitrile. 7.3 g di-tert-butyl-dicarbonate and 900 mg 4-dimethylaminopyridine are added thereto.

After stirring for 24 hours at ambient temperature the mixture is divided between 1 N HCl and ethyl acetate. The aqueous phase is extracted with

- 5 ethyl acetate and the combined organic phases are washed with saturated sodium hydrogen carbonate solution and saturated sodium chloride solution. After drying with magnesium sulphate the solvents are eliminated in vacuo. The residue is extracted from diisopropylether/petroleum ether. Yield: 6.6 g (82 % of theory)
- 10 Mass spectrum (ESI⁺): m/z = 265 [M+H]⁺

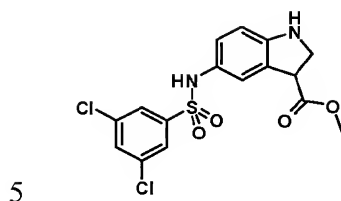
Example XV



- 15 3,5-dichloro-N-(2,3-dihydro-1H-indol-5-yl)-indolsulphonamide
4.08 g tert-butyl 5-(3,5-dichloro-phenylsulphonylamino)-2,3-dihydro-indole-1-carboxylate are dissolved in 70 ml dichloromethane. To this are added 25 ml trifluoroacetic acid and the solution is stirred for 2 hours at ambient temperature. The solvents are eliminated in vacuo and the residue is divided
- 20 between saturated sodium hydrogen carbonate solution and ethyl acetate. The aqueous phase is extracted with ethyl acetate and the combined organic phases are washed with saturated sodium chloride solution. After drying with magnesium sulphate the solvents are eliminated in vacuo. Yield: 3.0 g (97 % of theory)
- 25 Mass spectrum (ESI⁻): m/z = 341 [M-H]⁻

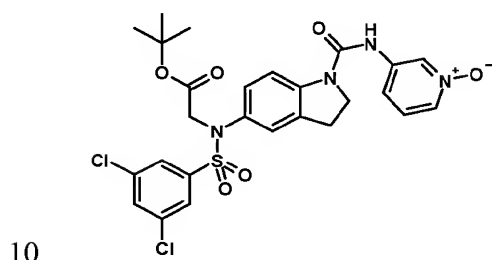
The following compounds are obtained analogously to Example XV:

- (1) methyl 5-(3,5-dichloro-phenylsulphonylamino)-2,3-dihydro-1H-indole-3-
- 30 carboxylate



R_f value: 0.50 (silica gel: petroleum ether/ethyl acetate 1:1)

Example XVI



tert. butyl {(3,5-dichloro-phenylsulphonyl)-[1-(1-oxy-pyridin-3-ylcarbamoyl)-2,3-dihydro-1H-indol-5-yl]-amino}-acetate

85 mg tert. butyl {(3,5-dichloro-phenylsulphonyl)-[1-(pyridin-3-ylcarbamoyl)-2,3-dihydro-1H-indol-5-yl]-amino}-acetate are dissolved in 3 ml

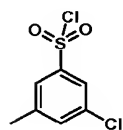
15 dichloromethane and 100 mg 3-chloro-perbenzoic acid are added. The mixture is stirred overnight at ambient temperature, diluted with ethyl acetate and washed with saturated sodium hydrogen carbonate solution and saturated sodium chloride solution. After drying with magnesium sulphate the solvents are eliminated in vacuo and the residue is chromatographed on silica
20 gel (dichloromethane/methanol 99:1 to 4:1).

Yield: 75 mg (86 % of theory)

Mass spectrum (ESI⁻): m/z = 591 [M-H]⁻

Example XVII

25

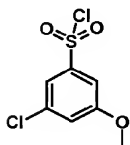


5 3-chloro-5-methyl-phenylsulphonyl-chloride

- 300 mg 3-chloro-5-methyl-phenylamine are dissolved in 1 ml concentrated HCl and cooled to 0°C . A solution of 170 mg sodium nitrite in 0.3 ml of water is added dropwise thereto. The solution thus prepared is added dropwise at 0°C to a solution of 85 mg copper-II-chloride, 0.3 ml of water and 7 ml sulphur dioxide in glacial acetic acid (30%). The cooling bath is removed and the mixture is stirred for another 20 minutes at ambient temperature. Then it is heated to 40°C for 10 minutes. It is then diluted with ice water, the solid is suction filtered and dried in the desiccator. The product is further reacted directly in Example XI without any further purification.
- 15 Yield: 370 mg (78 % of theory)

The following compounds are obtained analogously to Example XVII:

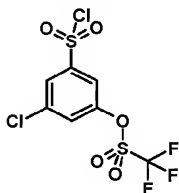
(1) 3-chloro-5-methoxy-phenylsulphonyl chloride



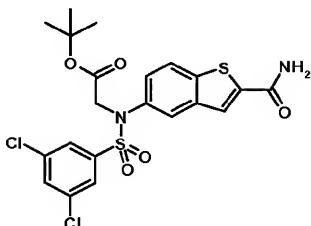
The aqueous phase is twice extracted with ethyl acetate. The combined organic phases are dried on magnesium sulphate and the solvent is eliminated in vacuo.

R_f value: 0.95 (silica gel; dichloromethane)

(2) 3-chloro-5-chlorosulphonyl-phenyl trifluoromethanesulphonate



The product is further reacted directly in Example XI(14) without any further purification.

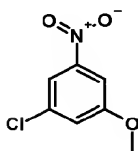
5 Example XVIII

tert. butyl [(2-carbamoyl-benzo[b]thiophene-5-yl)-(3,5-dichloro-phenylsulphonyl)-amino]-acetate

250 mg methyl 5-[tert-butoxycarbonylmethyl-(3,5-dichloro-phenylsulphonyl)-amino]-benzo[b]thiophen-2-carboxylate are dissolved in 30 ml ammonia-saturated methanol and stirred for 24 hours at ambient temperature. Then the solution is heated to 80°C in a pressurised vessel for 8 hours. Then the solvent is eliminated in vacuo and the residue is extracted from diisopropylether. The product thus obtained is chromatographed on silica gel with cyclohexane/ethyl acetate (9:1 to 1:4).

Yield: 141 mg (58 % of theory)

Mass spectrum (ESI⁺): m/z = 515 [M+H]⁺

20 Example IXX25 1-chloro-3-methoxy-5-nitro-benzene

10 g 3-chloro-5-nitrophenol are dissolved in 250 ml of ethanol. 11.9 g potassium carbonate and 6 ml dimethylsulphate are added and the mixture is stirred for 12 hours at ambient temperature. Then 3 ml of a 33 % ammonia solution are added and then the ethanol is eliminated in vacuo. The residue is

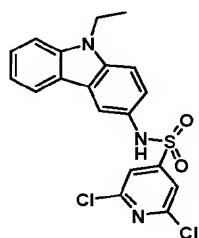
5 taken up in water and the precipitated solid is suction filtered and dried.

Yield: 10.37 g (96% of theory)

Mass spectrum (EI): $m/z = 187 [M]^+$

Example XX

10



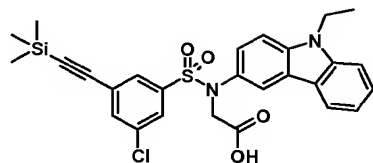
2,6-dichloro-pyridine-4-sulphonic acid-(9-ethyl-9H-carbazol-3-yl)-amide

2 g 4-amino-2,6-dichloropyridine are dissolved in 8 ml concentrated HCl and
15 cooled to 0°C . A solution of 900 mg sodium nitrite in 2 ml of water is added
dropwise thereto. The solution thus prepared is added dropwise at 0°C to a
solution of 550 mg copper-II-chloride, 1 ml of water and 10 ml sulphur dioxide
in glacial acetic acid (30%). The cooling bath is removed and the mixture is
stirred for 15 minutes at ambient temperature. Then it is diluted with ice water
20 and the solid is suction filtered. The aqueous phase is extracted with ethyl
acetate. The solid filtered off is dissolved in ethyl acetate. The combined
ethyl acetate phases are dried on magnesium sulphate and the solvent is
eliminated in vacuo. 1.2 g of (9-ethyl-9H-carbazol-3-yl)-methyl-amine and 15
ml of pyridine are added to the residue. The mixture is stirred for 12 hours at
25 ambient temperature, the solvent is eliminated in vacuo and the residue is
chromatographed on silica gel with dichloromethane.

Yield: 210 mg (10% of theory)

Mass spectrum (ESI⁻): $m/z = 418 [M-H]^-$

30

5 Example XXI

[(3-chloro-5-trimethylsilylethynyl-phenylsulphonyl)-(9-ethyl-9H-carbazol-3-yl)-amino]-acetic acid

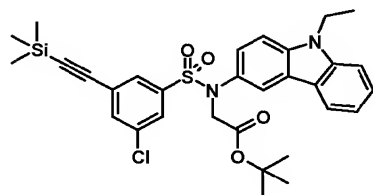
- 10 180 mg tert-butyl [(3-chloro-5-trimethylsilylethynyl-phenylsulphonyl)-(9-ethyl-9H-carbazol-3-yl)-amino]-acetate are dissolved in 5 ml dichloromethane. 1 ml of trifluoroacetic acid is added with stirring. The mixture is stirred overnight at ambient temperature and then the solvents are eliminated in vacuo. The residue is chromatographed on silica gel (dichloromethane/methanol 100:0 to
- 15 95:5).

Yield: 134 mg (74 % of theory)

Mass spectrum (ESI): $m/z = 537$ $[M-H]^-$

Example XXII

20



tert-butyl [(3-chloro-5-trimethylsilylethynyl-phenylsulphonyl)-(9-ethyl-9H-carbazol-3-yl)-amino]-acetate

- 320 mg tert-butyl [(3-chloro-5-trifluoromethylsulphonyloxy-phenylsulphonyl)-(9-ethyl-9H-carbazol-3-yl)-amino]-acetate are dissolved in 4 ml
- 25 dimethylformamide. 20 mg copper-I-iodide, 40 mg bis-triphenylphosphine-palladium-dichloride and 210 μ l trimethylsilylacetylene are added under argon. Then the mixture is heated to 60°C for 6 hours and then stirred overnight at ambient temperature. The mixture is then divided between saturated
- 30 potassium carbonate solution and ethyl acetate. The organic phase is dried

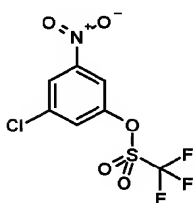
- 5 on magnesium sulphate and the solvents are eliminated in vacuo. The residue is chromatographed on silica gel (dichloromethane/methanol 100:0 to 95:5).

Yield: 223 mg (76 % of theory)

Mass spectrum (ESI⁺): m/z = 595 [M+H]⁺

10

Example XXIII



3-chloro-5-nitro-phenyl trifluoromethanesulphonate

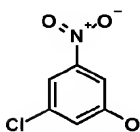
- 15 2.2 g 3-chloro-5-nitrophenol are dissolved in 30 ml dichloromethane, combined with 1.1 ml of pyridine and cooled to -10°C. A solution of 2.2 ml trifluoromethanesulphonic acid anhydride in 5 ml dichloromethane is added thereto, the mixture is left overnight to warm up to ambient temperature and then divided between dichloromethane and saturated sodium hydrogen
- 20 carbonate solution. The organic phase is washed with saturated sodium chloride solution and dried on magnesium sulphate. The solvent is eliminated in vacuo.

Yield: 3.5 g (81 % of theory)

R_f value: 0.90 (silica gel: dichloromethane)

25

Example XXIV



3-chloro-5-nitrophenol

- 30 1.65 g 3-chloro-5-nitroanisol are combined with 20.3 g pyridinium

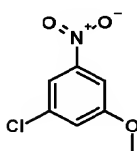
- 5 hydrochloride and heated to 200°C for 1 hour. Then the mixture is left overnight to come up to ambient temperature, 200 ml of water are added, the precipitated solid is suction filtered and dried in vacuo.

Yield: 860 mg (56 % of theory)

Mass spectrum (ESI): $m/z = 162 [M-H]^-$

10

Example XXV



3-chloro-5-nitroanisole

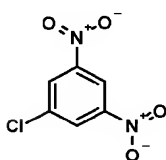
- 15 11.1 g 1-chloro-3,5-dinitrobenzene are dissolved in 100 ml of methanol and combined with 3 g sodium methoxide. Then the mixture is refluxed for 48 hours, cooled to ambient temperature and the solid is suction filtered.

Yield: 2.27 g (22 % of theory)

Mass spectrum (EI): $m/z = 187 [M]^+$

20

Example XXVI



1-chloro-3,5-dinitrobenzene

- 25 18 g 3,5-dinitroaniline are suspended in 45 ml concentrated hydrochloric acid and 15 ml of water and cooled to 0°C. A solution of 7.6 g sodium nitrite in 25 ml of water is added dropwise thereto. Then the diazonium salt solution thus obtained is added dropwise at 0°C to a solution of 13 g of copper-I-chloride in 45 ml concentrated hydrochloric acid. Then the mixture is refluxed for 10
- 30 minutes. After cooling to ambient temperature it is extracted 3 times with 150 ml of ethyl acetate and the combined organic phases are washed with water.

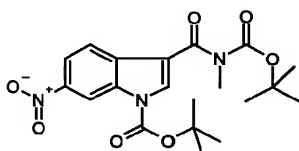
- 5 Then the mixture is dried on magnesium sulphate, the solvents are eliminated in vacuo and the residue is chromatographed on silica gel with petroleum ether/ ethyl acetate.

Yield: 11.15 g (58 % of theory)

Mass spectrum (EI): $m/z = 202$ $[M]^+$

10

Example XXVII



tert-butyl 3-(tert-butoxycarbonyl-methyl-aminocarbonyl)-6-nitro-indole-1-
15 carboxylate

220 mg of 6-nitro-1H-indole-3-carboxylic acid-methylamide are dissolved in 10 ml of tetrahydrofuran. 350 mg di-tert.-butyl-dicarbonate are added thereto and the mixture is stirred for 3 hours at ambient temperature. Then the solvent is eliminated in vacuo and the residue is chromatographed on silica gel

- 20 (cyclohexane/ethyl acetate 90:10 to 20:80)

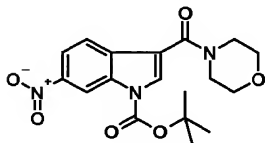
Yield: 95 mg (23 % of theory)

Mass spectrum (ESI⁺): $m/z = 420$ $[M+H]^+$

The following compounds are obtained analogously to Example XXVII:

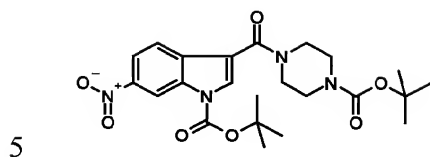
25

(1) tert-butyl 3-(morpholine-4-carbonyl)-6-nitro-indole-1-carboxylate



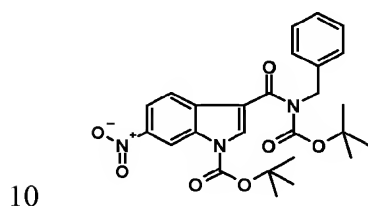
Mass spectrum (ESI⁺): $m/z = 376$ $[M+H]^+$

- 30 (2) tert-butyl 3-(4-tert-butoxycarbonyl-piperazine-1-carbonyl)-6-nitro-indole-1-carboxylate



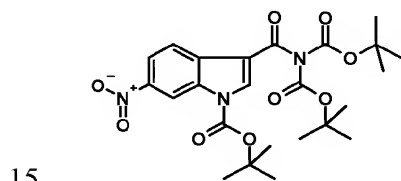
Mass spectrum (ESI⁺): m/z = 475 [M+H]⁺

(3) tert-butyl 3-(benzyl-tert-butoxycarbonyl-aminocarbonyl)-6-nitro-indole-1-carboxylate



Mass spectrum (ESI⁺): m/z = 496 [M+H]⁺

(4) tert-butyl 3-(bis-tert.-butoxycarbonyl)-aminocarbonyl-6-nitro-indole-1-carboxylate

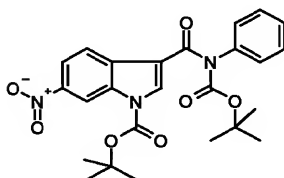


The reaction is carried out in the presence of a catalytic amount of 4-N,N-dimethylamino-pyridine at 60°C. The product is obtained in admixture with 3-(bis-tert.-butoxycarbonyl)-aminocarbonyl-6-nitro-1H-indole.

R_f value: 0.50 (silica gel; petroleum ether/ethyl acetate 4:1)

20

(5) tert-butyl 3-(tert-butoxycarbonyl-phenyl-aminocarbonyl)-6-nitro-indole-1-carboxylate



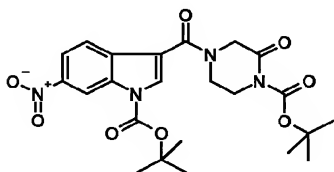
The reaction is carried out in the presence of a catalytic amount of 4-N,N-

5 dimethylamino-pyridine at 60°C.

R_f value: 0.39 (silica gel; petroleum ether/ethyl acetate 4:1)

Mass spectrum (ESI⁺): m/z = 482 [M+H]⁺

(6) tert-butyl 3-(4-tert-butoxycarbonyl-3-oxo-piperazine-1-carbonyl)-6-nitro-indole-1-carboxylate

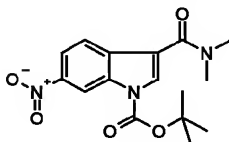


The reaction is carried out in the presence of a catalytic amount of 4-N,N-dimethylamino-pyridine at 60°C.

Mass spectrum (ESI⁺): m/z = 489 [M+H]⁺

15

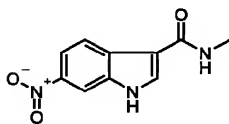
(7) tert-butyl 3-dimethylcarbamoyl-6-nitro-indole-1-carboxylate



The reaction is carried out in the presence of a catalytic amount of 4-N,N-dimethylamino-pyridine.

20 Mass spectrum (ESI⁺): m/z = 334 [M+H]⁺

Example XXVIII



25 6-nitro-1H-indole-3-carboxylic acid-methylamide

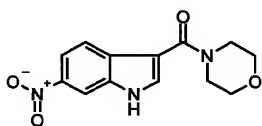
250 mg 6-nitro-1H-indole-3-carboxylic acid are dissolved in 10 ml of tetrahydrofuran, combined with 240 mg carbonyl-diimidazole and stirred for 30 minutes at 60°C. Then 750 µl of a 2 M solution of methylamine in tetrahydrofuran is added and the mixture is stirred overnight at 60°C. Then 1

- 5 N hydrochloric acid is added and the precipitated solid is suction filtered. Then the solid is extracted from ethyl acetate, suction filtered and dried. Yield: 225 mg (82 % of theory)

Mass spectrum (ESI⁺): m/z = 220 [M+H]⁺

- 10 The following compounds are obtained analogously to Example XXVIII:

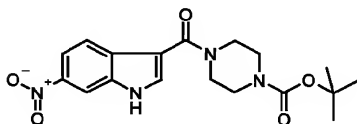
(1) morpholin-4-yl-(6-nitro-1H-indol-3-yl)-methanone



Mass spectrum (ESI⁺): m/z = 276 [M+H]⁺

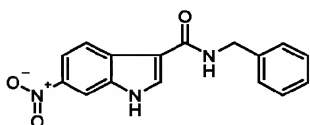
15

(2) tert-butyl 4-(6-nitro-1H-indole-3-carbonyl)-piperazine-1-carboxylate



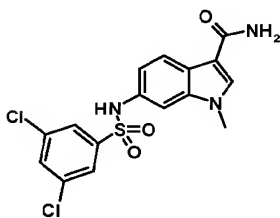
Mass spectrum (ESI⁻): m/z = 373 [M-H]⁻

- 20 (3) 6-nitro-1H-indole-3-carboxylic acid-benzylamide



Mass spectrum (ESI⁺): m/z = 296 [M+H]⁺

- 25 (4) 6-(3,5-dichloro-phenylsulphonylamino)-1-methyl-1H-indole-3-carboxylic acid-amide

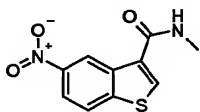


The crude product is chromatographed on silica gel (cyclohexane/ethyl

5 acetate 40:60 to 0:100).

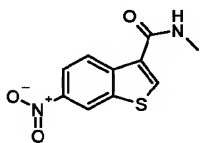
Mass spectrum (ESI⁺): m/z = 398 [M+H]⁺

(5) 5-nitro-benzo[b]thiophene-3-carboxylic acid-methylamide



10 Mass spectrum (ESI⁺): m/z = 237 [M+H]⁺

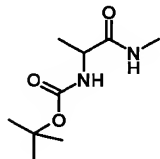
(6) 6-nitro-benzo[b]thiophene-3-carboxylic acid-methylamide



Mass spectrum (ESI⁺): m/z = 237 [M+H]⁺

15

(7) tert. butyl (1-methylcarbamoyl-ethyl)-carbamate

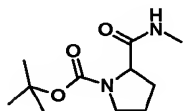


After the reaction has ended the mixture is diluted with ethyl acetate, washed with 1 M phosphoric acid solution and dried on magnesium sulphate. The

20 solvents are then eliminated in vacuo.

Mass spectrum (ESI⁺): m/z = 203 [M+H]⁺

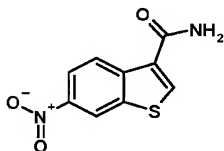
(8) tert-butyl 2-methylcarbamoyl-pyrrolidine-1-carboxylate



25 After the reaction has ended the mixture is divided between ethyl acetate and 1 M phosphoric acid solution. The organic phase is washed with 1 M sodium hydroxide solution and dried on magnesium sulphate. The solvents are eliminated in vacuo.

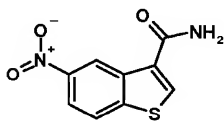
- 5 Mass spectrum (ESI⁺): m/z = 229 [M+H]⁺

(9) 6-nitro-benzo[b]thiophene-3-carboxylic acid-amide



and

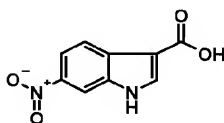
- 10 5-nitro-benzo[b]thiophene-3-carboxylic acid-amide



are obtained as a mixture during the reaction of a mixture of 6-nitro-benzo[b]-thiophene-3-carboxylic acid and 5-nitro-benzo[b]thiophene-3-carboxylic acid (Example XLV). The crude product is chromatographed on silica gel, while

- 15 the two products are obtained as a mixture and further reacted directly in Example XII (30).

Example XXIX



20

6-nitro-1H-indole-3-carboxylic acid

3.7 g 2,2,2-trifluoro-1-(6-nitro-1H-indol-3-yl)-ethanone are combined with 20 ml of a 40 % sodium hydroxide solution and refluxed for 4 hours.

After cooling to 0°C the mixture is diluted with a little water and adjusted to pH

- 25 1 by the careful addition of concentrated hydrochloric acid. The precipitated solid is suction filtered and dissolved in dichloromethane/methanol 10:1. After drying with magnesium sulphate the solvents are eliminated in vacuo and the residue is extracted from diethyl ether.

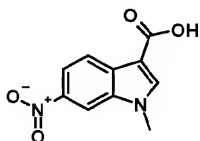
Yield: 3 g (100 % of theory)

- 30 Mass spectrum (ESI⁻): m/z = 205 [M-H]⁻

5

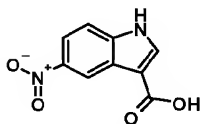
The following compounds are obtained analogously to Example XXIX:

(1) 1-methyl-6-nitro-1H-indole-3-carboxylic acid



10 Mass spectrum (ESI⁻): m/z = 219 [M-H]⁻

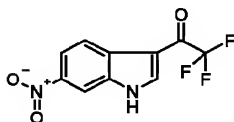
(2) 5-nitro-1H-indole-3-carboxylic acid



R_f value: 0.30 (silica gel: dichloromethane/methanol 10:1)

15

Example XXX



2,2,2-trifluoro-1-(6-nitro-1H-indol-3-yl)-ethanone

20 2.5 g 6-nitro-1H-indole are dissolved in 10 ml dimethylformamide. 5 ml trifluoroacetic anhydride are added thereto and the mixture is heated to 60°C for 3 hours. Then the mixture is diluted with ethyl acetate and the organic phase is washed with saturated sodium hydrogen carbonate solution and with saturated sodium chloride solution. After drying with magnesium sulphate the
25 solvents are eliminated in vacuo and the residue is extracted from dichloromethane.

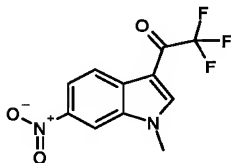
Yield: 3.7 g (96 % of theory)

Mass spectrum (ESI⁻): m/z = 257 [M-H]⁻

30 The following compounds are obtained analogously to Example XXX:

5

(1) 2,2,2-trifluoro-1-(1-methyl-6-nitro-1H-indol-3-yl)-ethanone

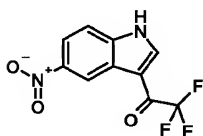


Tetrahydrofuran is used as solvent.

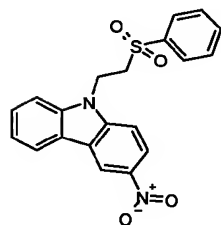
Mass spectrum (ESI⁻): m/z = 317 [M-HCOO]⁻

10

(2) 2,2,2-trifluoro-1-(5-nitro-1H-indol-3-yl)-ethanone



The reaction is carried out overnight at ambient temperature. The product is extracted from ethyl acetate.

15 R_f value: 0.50 (silica gel: petroleum ether/ethyl acetate 1:1)Example XXXI20 9-(2-phenylsulphonyl-ethyl)-3-nitro-9H-carbazole

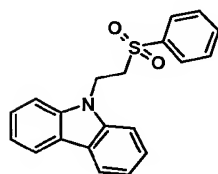
3.39 g 9-(2-phenylsulphonyl-ethyl)-9H-carbazole are dissolved in 120 ml acetonitrile, and combined with 6.4 g ammonium-cerium-nitrate and 5 g silica gel. Then the mixture is heated to 70°C for 4 hours, filtered hot and the solid is washed with hot acetonitrile. The mother liquor is freed from the solvent in vacuo and the residue is chromatographed on silica gel (dichloromethane/methanol 100:0 to 98:2).

25

Yield: 1.53 g (40 % of theory)

- 5 Mass spectrum (ESI⁺): m/z = 381 [M+H]⁺

Example XXXII



- 10 9-(2-phenylsulphonyl-ethyl)-9H-carbazole

1.8 g 9H-carbazole and 9.8 g phenylvinylsulphone are suspended in 3 ml of tetrahydrofuran, cooled to 0°C, combined with 60 µl

benzyltrimethylammonium hydroxide (40 % solution in water) and stirred for 20 minutes. Then the mixture is heated to 115°C for 7 hours. Then it is

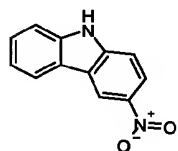
- 15 divided between ethyl acetate and 1 N hydrochloric acid, the organic phase is dried on magnesium sulphate and the solvent is eliminated in vacuo. The residue is chromatographed on silica gel (cyclohexane/ethyl acetate 2:1).

Yield: 2.35 g (65 % of theory)

Mass spectrum (ESI⁺): m/z = 336 [M+H]⁺

20

Example XXXIII



3-nitro-9H-carbazole

- 25 2.2 g 9-(2-phenylsulphonyl-ethyl)-3-nitro-9H-carbazole are dissolved in 40 ml of tetrahydrofuran, combined with 700 mg potassium-tert.-butoxide and stirred for 2 hours at ambient temperature. A further 100 mg potassium-tert.-butoxide are added and the mixture is stirred for 4 hours at ambient temperature. Then another 100 mg potassium-tert.-butoxide are added. The
- 30 mixture is heated for 2 hours to 50°C, divided between ethyl acetate and 1 N hydrochloric acid, the organic phase is washed with saturated sodium chloride

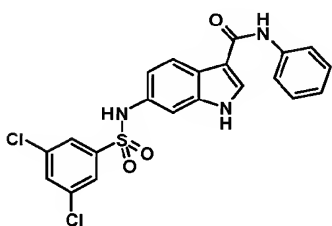
5 solution and dried with magnesium sulphate. After elimination of the solvents in vacuo the residue is chromatographed on silica gel (cyclohexane/ethyl acetate 90:10 to 80:20).

Yield: 900 mg (73 % of theory)

Mass spectrum (ESI⁺): m/z = 213 [M+H]⁺

10

Example XXXIV



6-(3,5-dichloro-phenylsulphonylamino)-1H-indole-3-carboxylic acid-phenylamide

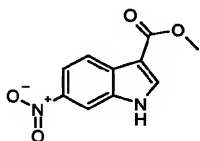
15

100 mg methyl 6-(3,5-dichloro-phenylsulphonylamino)-1H-indole-3-carboxylate are dissolved in 5 ml of methanol, combined with 2 ml 1 N sodium hydroxide solution and stirred for 2 hours at ambient temperature. Then the mixture is divided between ethyl acetate and 2 N hydrochloric acid, the aqueous phase is extracted twice with ethyl acetate and the combined organic phases are dried on sodium sulphate. The solvents are eliminated in vacuo and the residue is taken up in 3 ml dimethylformamide. 114 mg O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium-hexafluorophosphate (HATU) and 65 µl N,N-diisopropyl-N-ethyl-amine are added and the mixture is stirred for 3 hours at 50°C. Then it is divided between water and ethyl acetate, the aqueous phase is extracted twice with ethyl acetate and the combined organic phases are dried on sodium sulphate. After elimination of the solvents in vacuo the residue is chromatographed on silica gel (cyclohexane/ethyl acetate 90:10 to 20:80). The product thus obtained is further reacted directly in VI (28).

20

25

30

5 Example XXXVmethyl 6-nitro-1H-indole-3-carboxylate

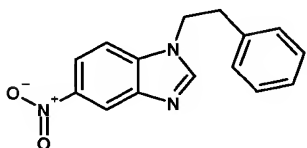
1 g methyl 1H-indole-3-carboxylate is dissolved in 5 ml acetic acid, combined
10 with 500 µl concentrated nitric acid (>90%) and heated to 60°C for 1 hour.

The mixture is divided between water and dichloromethane and the aqueous
phase is extracted twice with dichloromethane. The combined organic
phases are dried on sodium sulphate, freed from the solvent in vacuo and the
residue is chromatographed on silica gel (cyclohexane/ethyl acetate 90:10 to
15 40:60).

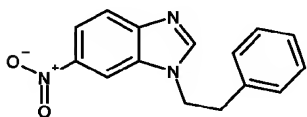
Yield: 290 mg (23 % of theory)

Mass spectrum (ESI⁻): m/z = 219 [M-H]⁻

In addition 275 mg of methyl 4-nitro-1H-indole-3-carboxylate are obtained.

20 Example XXXVI5-nitro-1-(phenylethyl)-1H-benzimidazole

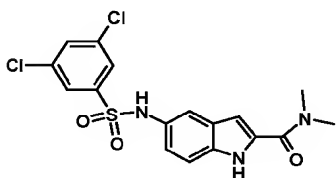
25 and

6-nitro-1-(phenylethyl)-1H-benzimidazole

1 g 5-nitro-1H-benzimidazole is dissolved in 10 ml dimethylformamide and
30 combined with 270 mg NaH (60 % in mineral oil). The mixture is left for 1

- 5 hour with stirring and 1 ml phenylethylbromide is added. Then the mixture is stirred for 3 hours at ambient temperature and divided between saturated ammonium chloride solution and ethyl acetate. The aqueous phase is extracted with ethyl acetate and the combined organic phases are dried on magnesium sulphate. After elimination of the solvents in vacuo the residue is
- 10 chromatographed on silica gel (cyclohexane/ethyl acetate 90:10 to 60:40). Yield: 820 mg (50 % of theory) as an isomer mixture of 5-nitro-1-(phenylethyl)-1H-benzimidazole and 6-nitro-1-(phenylethyl)-1H-benzimidazole
- Mass spectrum (ESI⁺): m/z = 268 [M+H]⁺

15 Example XXXVII



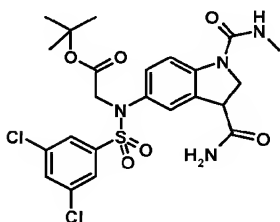
5-(3,5-dichloro-phenylsulphonylamino)-1H-indol-2-carboxylic acid-
dimethylamide

- 20 55 mg 5-(3,5-dichloro-phenylsulphonylamino)-1H-indole-2-carboxylic acid are dissolved in 2 ml of tetrahydrofuran, combined with 25 mg carbonyldiimidazole, stirred for 3 hours at ambient temperature and for 1 hour at 40°C. Then the mixture is combined with 300 µl dimethylamine (2 M in tetrahydrofuran) and stirred overnight. The solvent is eliminated in vacuo and
- 25 the residue is divided between ethyl acetate and 0.5 N hydrochloric acid. The organic phase is washed with water and saturated sodium chloride solution and dried on magnesium sulphate. After elimination of the solvents in vacuo the residue is chromatographed on silica gel (cyclohexane/ethyl acetate 90:10 to 30:70).
- 30 Yield: 26 mg (44 % of theory)
- Mass spectrum (ESI⁻): m/z = 410 [M-H]⁻

The following compounds are obtained analogously to Example XXXVII:

5

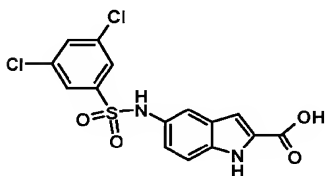
(1) tert. butyl [(3-carbamoyl-1-methylcarbamoyl-2,3-dihydro-1H-indol-5-yl)-(3,5-dichloro-phenylsulphonyl)-amino]-acetate



To form the imidazolidine the mixture is heated to 60°C for 1 hour. To form the methylamide the mixture is heated to 60°C overnight. After the reaction has ended the mixture is divided between ethyl acetate and water and the organic phase is washed with saturated sodium chloride solution.

Mass spectrum (ESI⁺): m/z = 557 [M+H]⁺

15 Example XXXVIII

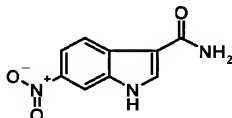


5-(3,5-dichloro-phenylsulphonylamino)-1H-indol-2-carboxylic acid

100 mg ethyl 5-(3,5-dichloro-phenylsulphonylamino)-1H-indole-2-carboxylate are dissolved in 2 ml of tetrahydrofuran and combined with 2 ml of 1 N sodium hydroxide solution. The mixture is stirred for 48 hours at ambient temperature, the tetrahydrofuran is eliminated in vacuo, the residue is diluted with water, and 1 N hydrochloric acid is added until the pH is 2. The precipitated solid is suction filtered, washed with water and dried in vacuo.

25 Yield: 60 mg (64 % of theory)

Mass spectrum (ESI⁻): m/z = 383 [M-H]⁻

5 Example XXXIX6-nitro-1H-indole-3-carboxylic acid-amide

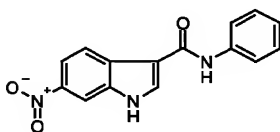
- 250 mg 6-nitro-1H-indole-3-carboxylic acid are dissolved in 10 ml of toluene,
10 combined with 3 ml of thionyl chloride and refluxed for 1 hour. Then the
volatile constituents are eliminated in vacuo, the residue is taken up in
dichloromethane and this is in turn eliminated in vacuo. Then it is taken up in
10 ml of tetrahydrofuran, combined with 6 ml of a 0.5 M solution of ammonia
in dioxane and heated to 60°C for 12 hours. The solvents are eliminated in
15 vacuo, the residue is extracted from 1 N hydrochloric acid and the solid
obtained is suction filtered and dried in vacuo.

Yield: 230 mg (92 % of theory)

Mass spectrum (ESI⁺): m/z = 206 [M+H]⁺

- 20 The following compounds are obtained analogously to Example XXXIX:

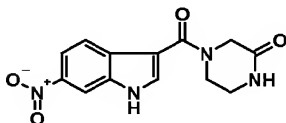
(1) 6-nitro-1H-indole-3-carboxylic acid-phenylamide



Mass spectrum (ESI⁺): m/z = 282 [M+H]⁺

25

(2) 4-(6-nitro-1H-indole-3-carbonyl)-piperazin-2-one

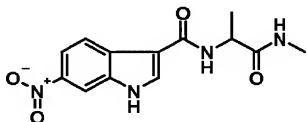


The acid chloride formed is reacted in dichloromethane with 2-oxo-piperazine
in the presence of 1 equivalent of pyridine.

- 30 Mass spectrum (ESI⁻): m/z = 287 [M-H]⁻

5

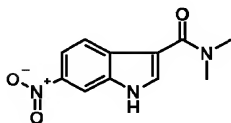
(3) 6-nitro-1H-indole-3-carboxylic acid-(1-methylcarbamoyl-ethyl)-amide



The acid chloride formed is reacted in dichloromethane with 2-oxo-piperazine in the presence of 1 equivalent of pyridine.

10 Mass spectrum (ESI⁺): m/z = 291 [M+H]⁺

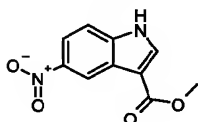
(4) 6-nitro-1H-indole-3-carboxylic acid-dimethylamide



The acid chloride formed is reacted in dichloromethane with dimethylamine (2M in tetrahydrofuran) in the presence of 1 equivalent of pyridine.

15 Mass spectrum (ESI⁺): m/z = 234 [M+H]⁺

(5) methyl 5-nitro-1H-indole-3-carboxylate

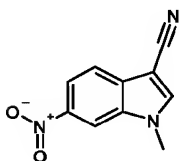


20 During the formation of the acid chloride, 2 drops of dimethylformamide are added and the mixture is refluxed for 5 hours. To form the methylester the mixture is refluxed in methanol for 5 hours. After cooling to ambient temperature the precipitated solid is suction filtered and dried in vacuo.

R_f value: 0.40 (silica gel: dichloromethane/methanol 40:1)

25

Example XL

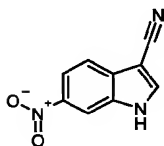


5 1-methyl-6-nitro-1H-indole-3-carbonitrile

1.6 g 6-nitro-1H-indole-3-carbonitrile are dissolved in 45 ml of tetrahydrofuran, combined with 1 g potassium-tert.-butoxide and stirred for 30 minutes. Then a solution of 560 µl methyl iodide in 5 ml of tetrahydrofuran is slowly added dropwise and the mixture is stirred for 5 hours. The solvents are eliminated in vacuo, water is added and the pH is adjusted to 4 by the addition of citric acid.

10 The solid is suction filtered and washed with water and some cold methanol. Yield: 1.59 g (65 % of theory)

Mass spectrum (ESI⁺): m/z = 219 [M+NH₄]⁺

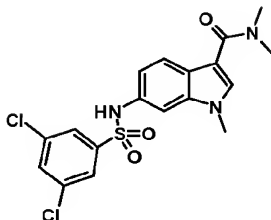
15 Example XLI6-nitro-1H-indole-3-carbonitrile

6.1 g 6-nitro-1H-indole are dissolved in 100 ml acetonitrile and cooled to 0°C .

20 A solution of 3.2 ml chlorosulphonyl isocyanate in 25 ml acetonitrile is added dropwise and the mixture is stirred for 2 hours. Then a solution of 5 ml triethylamine in 25 ml acetonitrile is added dropwise. The mixture is stirred for 1 hour at ambient temperature and for 50 minutes at 80°C. Then the solvents are eliminated in vacuo, the residue is extracted from cold water, the solid is suction filtered and washed successively with water, saturated sodium hydrogen carbonate solution and water. The solid thus obtained is dried in the desiccator. Then the solid is taken up in 500 ml dichloromethane/methanol 95:5 and stirred with some aluminium oxide. It is suction filtered through a thin layer of aluminium oxide and washed with 400 ml dichloromethane/methanol 95:5. The filtrate is evaporated down in vacuo and the residue is dried in vacuo.

25 Yield: 2.76 g (40 % of theory)

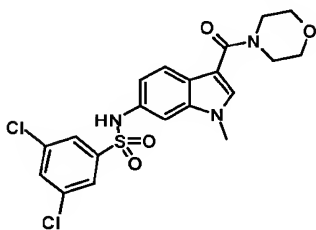
30 Mass spectrum (ESI⁻): m/z = 186 [M-H]⁻

5 Example XLII6-(3,5-dichloro-phenylsulphonylamino)-1-methyl-1H-indole-3-carboxylic acid-dimethylamide

- 10 300 mg 6-(3,5-dichloro-phenylsulphonylamino)-1-methyl-1H-indole-3-carboxylic acid are dissolved in 2 ml dimethylformamide, combined with 319 μ l N,N-diisopropyl-N-ethyl-amine and 241 mg O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium-tetrafluoroborate (TBTU) and stirred for 15 minutes at ambient temperature. 751 μ l of a 2 M solution of dimethylamine in
- 15 tetrahydrofuran are added and the mixture is stirred overnight at ambient temperature. Then it is divided between water and ethyl acetate, the aqueous phase is extracted with ethyl acetate and the combined organic phases are dried on magnesium sulphate. The solvents are eliminated in vacuo.
- Yield: 360 mg (112 % of theory)
- 20 Mass spectrum (ESI^-): $m/z = 424$ $[\text{M-H}]^-$

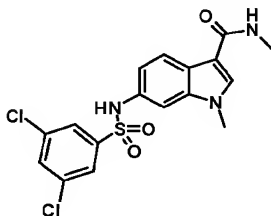
The following compounds are obtained analogously to Example XLII:

- (1) 3,5-dichloro-N-[1-methyl-3-(morpholine-4-carbonyl)-1H-indol-6-yl]-
- 25 phenylsulphonamide



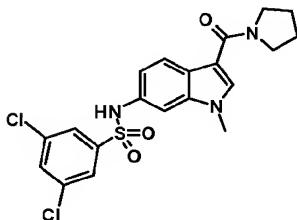
Mass spectrum (ESI^-): $m/z = 466$ $[\text{M-H}]^-$

- 5 (2) 6-(3,5-dichloro-phenylsulphonylamino)-1-methyl-1H-indole-3-carboxylic acid-methylamide



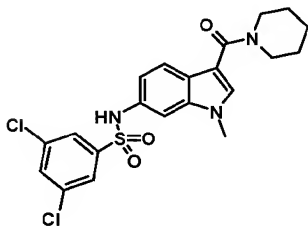
Mass spectrum (ESI⁻): m/z = 410 [M-H]⁻

- 10 (3) 3,5-dichloro-N-[1-methyl-3-(pyrrolidine-1-carbonyl)-1H-indol-6-yl]-phenylsulphonamide



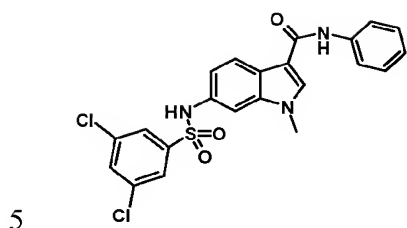
Mass spectrum (ESI⁻): m/z = 450 [M-H]⁻

- 15 (4) 3,5-dichloro-N-[1-methyl-3-(piperidine-1-carbonyl)-1H-indol-6-yl]-phenylsulphonamide



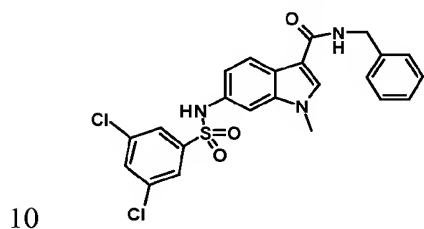
Mass spectrum (ESI⁻): m/z = 464 [M-H]⁻

- 20 (5) 6-(3,5-dichloro-phenylsulphonylamino)-1-methyl-1H-indole-3-carboxylic acid-phenylamide



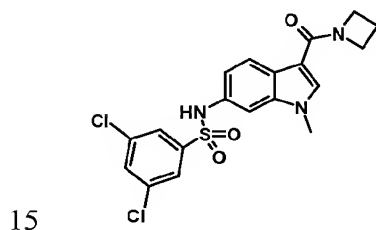
Mass spectrum (ESI⁻): m/z = 472 [M-H]⁻

(6) 6-(3,5-dichloro-phenylsulphonylamino)-1-methyl-1H-indole-3-carboxylic acid-benzylamide



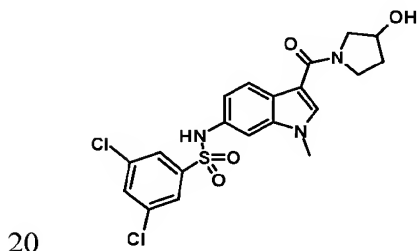
Mass spectrum (ESI⁻): m/z = 486 [M-H]⁻

(7) N-[3-(azetidine-1-carbonyl)-1-methyl-1H-indol-6-yl]-3,5-dichloro-phenylsulphonamide



Mass spectrum (ESI⁺): m/z = 438 [M+H]⁺

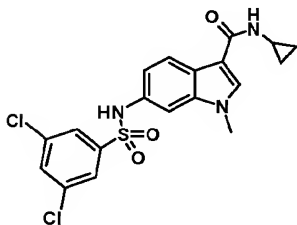
(8) 3,5-dichloro-N-[3-(3-hydroxy-pyrrolidine-1-carbonyl)-1-methyl-1H-indol-6-yl]-phenylsulphonamide



Mass spectrum (ESI⁺): m/z = 468 [M+H]⁺

5

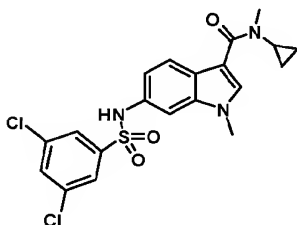
(9) 6-(3,5-dichloro-phenylsulphonylamino)-1-methyl-1H-indole-3-carboxylic acid-cyclopropylamide



R_f value: 0.34 (silica gel: petroleum ether/ethyl acetate 1:2)

10

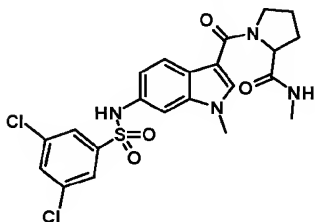
(10) 6-(3,5-dichloro-phenylsulphonylamino)-1-methyl-1H-indole-3-carboxylic acid-cyclopropyl-methyl-amide



Mass spectrum (ESI⁺): m/z = 452 [M+H]⁺

15

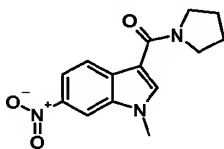
(11) 1-[6-(3,5-dichloro-phenylsulphonylamino)-1-methyl-1H-indole-3-carbonyl]-pyrrolidin-2-carboxylic acid-methylamide



Mass spectrum (ESI⁺): m/z = 509 [M+H]⁺

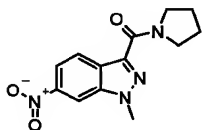
20

(12) (1-methyl-6-nitro-1H-indol-3-yl)-pyrrolidin-1-yl-methanone



5 Mass spectrum (ESI⁺): m/z = 274 [M+H]⁺

(13) (1-methyl-6-nitro-1H-indazol-3-yl)-pyrrolidin-1-yl-methanone



Obtained during the reaction of a mixture of 1-methyl-6-nitro-1H-indazole-3-
10 carboxylic acid and 2-methyl-6-nitro-2H-indazole-3-carboxylic acid. The
product is purified by chromatography on silica gel.

Mass spectrum (ESI⁺): m/z = 275 [M+H]⁺

(14) 1-methyl-6-nitro-1H-indazole-3-carboxylic acid-methylamide

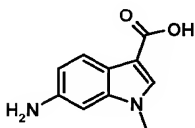


15 Obtained during the reaction of a mixture of 1-methyl-6-nitro-1H-indazole-3-
carboxylic acid and 2-methyl-6-nitro-2H-indazole-3-carboxylic acid. The
product is purified by chromatography on silica gel.

Mass spectrum (ESI⁺): m/z = 235 [M+H]⁺

20

Example XLIII



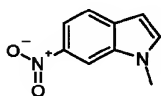
6-amino-1-methyl-1H-indole-3-carboxylic acid

25 12 g 6-nitro-1-methyl-1H-indole-3-carboxylic acid are dissolved in 500 ml of
water, 60 ml 1 N sodium hydroxide solution and 30 ml of methanol. 1.2 g
Raney nickel are added and the mixture is hydrogenated for 26 hours at 1.5
bar. Then the catalyst is filtered off and the solvent is eliminated in vacuo.
The residue is suspended in 100 ml of pyridine. 16.3 g 3,5-
30 dichlorophenylsulphonyl chloride are added and the mixture is stirred

- 5 overnight at ambient temperature. The pyridine is eliminated in vacuo. The residue is divided between water and ethyl acetate and the pH is adjusted to 5 by the addition of citric acid. The aqueous phase is extracted 3 times with ethyl acetate and the combined organic phases are dried on magnesium sulphate. After elimination of the solvents the residue is chromatographed on
10 silica gel (dichloromethane/methanol/acetic acid 95:5:1 to 89:10:1)
Yield: 2.5 g (9 % of theory)
Mass spectrum (ESI⁻): m/z = 397 [M-H]⁻

Example XLIV

15



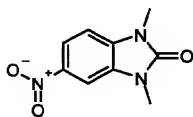
1-methyl-6-nitro-1H-indole

- 4 g of 6-nitro-1H-indole are added batchwise at 0°C to 800 mg sodium hydride (60 % in mineral oil) in 20 mg dimethylformamide. The mixture is stirred for
20 10 minutes, then 1.86 ml methyl iodide are added dropwise and the mixture is left overnight to come up to ambient temperature. Then it is divided between water and ethyl acetate, the aqueous phase is extracted with ethyl acetate and the combined organic phases are washed with saturated sodium chloride solution. After drying with magnesium sulphate the solvents are eliminated in
25 vacuo.
Yield: 4.54 g (104 % of theory)
Mass spectrum (ESI⁺): m/z = 177 [M+H]⁺

The following compounds are obtained analogously to Example XLIV:

30

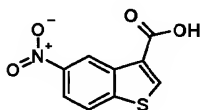
(1) 1,3-dimethyl-5-nitro-1,3-dihydro-benzimidazol-2-one



The product is extracted from ethyl acetate/methanol 95:5.

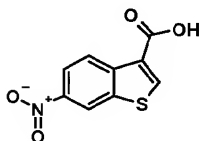
- 5 Mass spectrum (ESI⁺): m/z = 208 [M+H]⁺

Example XLV



- 10 5-nitro-benzo[b]thiophene-3-carboxylic acid

and

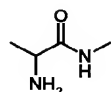


- 15 6-nitro-benzo[b]thiophene-3-carboxylic acid

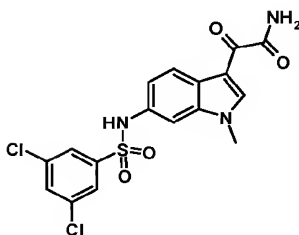
- 2 g benzo[b]thiophene-3-carboxylic acid are dissolved in 11 ml acetic anhydride and cooled to 0°C. A solution of 4.4 ml concentrated nitric acid in 10 ml acetic acid is added dropwise, while not allowing the temperature to rise above 5°C. Then the mixture is stirred for 1.5 hours and then combined with
- 20 200 ml ice water. The solid is suction filtered and dried in vacuo. Then it is dissolved in hot ethanol. After cooling to ambient temperature the solid (5-nitro-benzo[b]thiophene-3-carboxylic acid, approximately 80 %) is suction filtered. By elimination of the solvent in vacuo, 6-nitro-benzo[b]thiophene-3-carboxylic acid (approx. 66 %) is obtained from the mother liquor.
- 25 Yield: 250 mg (10 % of theory, about 80 %) 5-nitro-benzo[b]thiophene-3-carboxylic acid
- Mass spectrum (ESI⁻): m/z = 222 [M-H]⁻
- Yield: 624 mg (25 % of theory, about 66 %) 6-nitro-benzo[b]thiophene-3-carboxylic acid
- 30 Mass spectrum (ESI⁻): m/z = 222 [M-H]⁻

Example XLVI

5

2-amino-N-methyl-propionamide

- 2 g tert. butyl (1-methylcarbamoyl-ethyl)-carbamate are dissolved in 20 ml dichloromethane, combined with 3.7 ml of a 4 M solution of hydrogen chloride
10 in dioxane and stirred for 24 hours at ambient temperature. The solvents are eliminated in vacuo and the residue is divided between 10 ml 1 N sodium hydroxide solution and dichloromethane. The aqueous phase is extracted with dichloromethane and the combined organic phases are dried on magnesium sulphate. The solvents are eliminated in vacuo.
- 15 Yield: 400 mg (40 % of theory)
Mass spectrum (ESI⁺): m/z = 103 [M+H]⁺

Example XLVII

20

2-[6-(3,5-dichloro-phenylsulphonylamino)-1-methyl-1H-indol-3-yl]-2-oxoacetamide

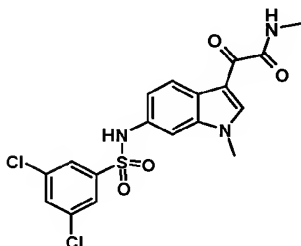
- 400 mg [6-(3,5-dichloro-phenylsulphonylamino)-1-methyl-1H-indol-3-yl]-oxoacetyl-chloride are dissolved in 1.5 ml tetrahydrofuran, combined with 550 µl
25 concentrated ammonia (32 % solution in water) and stirred for 3.5 hours. The solvent is eliminated in vacuo and the residue is extracted from a little methanol. The solid is suction filtered and dried in vacuo.
- Yield: 140 mg (37 % of theory)
Mass spectrum (ESI⁺): m/z = 426 [M+H]⁺

30

The following compounds are obtained analogously to Example XLVII:

5

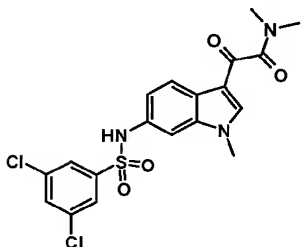
(1) 2-[6-(3,5-dichloro-phenylsulphonylamino)-1-methyl-1H-indol-3-yl]-N-methyl-2-oxo-acetamide



Mass spectrum (ESI⁻): m/z = 438 [M-H]⁻

10

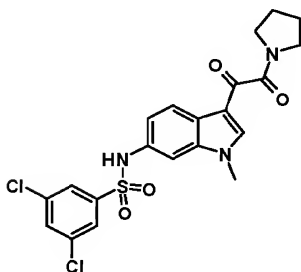
(2) 2-[6-(3,5-dichloro-phenylsulphonylamino)-1-methyl-1H-indol-3-yl]-N,N-dimethyl-2-oxo-acetamide



Mass spectrum (ESI⁺): m/z = 454 [M+H]⁺

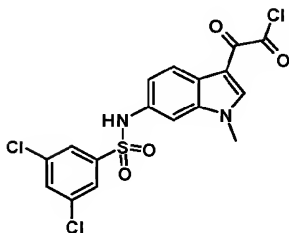
15

(3) 3,5-dichloro-N-[1-methyl-3-(2-oxo-2-pyrrolidin-1-yl-acetyl)-1H-indol-6-yl]-phenylsulphonamide

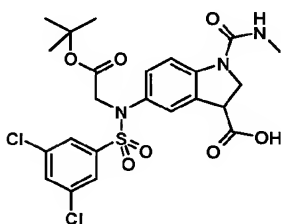


Mass spectrum (ESI⁺): m/z = 480 [M+H]⁺

20

5 Example XLVIII6-(3,5-dichloro-phenylsulphonylamino)-1-methyl-1H-indol-3-yl-oxo-acetyl-chloride

- 10 1.1 g 3,5-dichloro-N-(1-methyl-1H-indol-6-yl)-phenylsulphonamide are dissolved in 15 ml diethyl ether, cooled to 0°C and combined with 296 µl oxalyl chloride. Then the mixture is stirred for 2 hours at 0°C and for 12 hours at ambient temp. The solvents are distilled off at 50°C. The crude product thus obtained is further reacted directly (XLVII).
- 15 Yield: 1.34 g (96 % of theory)

Example XLIX

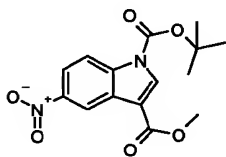
- 20 5-[tert-butoxycarbonylmethyl-(3,5-dichloro-phenylsulphonyl)-amino]-1-methylcarbamoyl-2,3-dihydro-1H-indole-3-carboxylic acid
- 100 mg methyl 5-[tert-butoxycarbonylmethyl-(3,5-dichloro-phenylsulphonyl)-amino]-1-methylcarbamoyl-2,3-dihydro-1H-indole-3-carboxylate are dissolved in 1.2 ml of tetrahydrofuran, combined with 349 µl of a 1 M solution of lithium
- 25 hydroxide in water and stirred overnight at ambient temperature. Then the mixture is cooled to 0°C, combined with 350 µl 1 M hydrochloric acid and divided between ethyl acetate and saturated sodium chloride solution. The organic phase is dried on magnesium sulphate and the solvents are

- 5 eliminated in vacuo. The residue is chromatographed on silica gel (dichloromethane/methanol 20:1).

Yield: 40 mg (41 % of theory)

Mass spectrum (ESI⁺): m/z = 558 [M+H]⁺

10 Example L



1-tert-butyl-3-methyl 5-nitro-indole-1,3-dicarboxylate

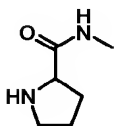
- 5.9 g methyl 5-nitro-1H-indole-3-carboxylate are dissolved in 100 ml
15 acetonitrile, combined with 100 mg N,N-dimethylamino-pyridine and a solution of 6.4 g di-tert.-butyl-dicarbonate in 20 ml of tetrahydrofuran is added dropwise thereto. The mixture is stirred overnight at ambient temperature, then heated to 30°C for 30 minutes and cooled to 0°C. The solid thus precipitated is suction filtered. The mother liquor is freed from the solvents in
20 vacuo and the residue is extracted from petroleum ether/ethyl acetate.

Yield: 7.4 g (86 % of theory)

R_f value: 0.50 (silica gel: petroleum ether/ethyl acetate 3:1)

Example LI

25



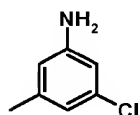
pyrrolidine-2-carboxylic acid-methylamide · CF₃CO₂H

- 200 mg tert-butyl 2-methylcarbamoyl-pyrrolidine-1-carboxylate are dissolved
in 2 ml dichloromethane, combined with 1 ml trifluoroacetic acid and stirred for
30 2 hours at ambient temperature. Then the volatile constituents are eliminated in vacuo, the residue is dissolved in dichloromethane and diethyl ether and

- 5 combined with some activated charcoal. Then the solution is filtered, evaporated down in vacuo and the residue is dried in vacuo. The product thus obtained is further reacted directly in V (8).

Example LII

10



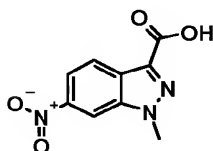
3-chloro-5-methyl-aniline

- 2.4 g of 3-chloro-5-nitro-toluene are dissolved in 35 ml of ethanol, combined with 15.8 g tin dichloride-dihydrate and refluxed for 3 hours. The solvent is eliminated in vacuo, the residue is taken up in 4 M sodium hydroxide solution and filtered through kieselguhr. The filter cake is washed thoroughly with ethyl acetate. The aqueous phase is extracted 3 times with ethyl acetate and the combined organic phases are washed with saturated sodium chloride solution and dried on magnesium sulphate. The solvent is eliminated in vacuo and the residue is chromatographed on silica gel (cyclohexane/ethyl acetate 81:15 to 70:30).

Yield: 1.59 g (80 % of theory)

Mass spectrum (ESI⁺): m/z = 142 [M+H]⁺

25 Example LIII



1-methyl-6-nitro-1H-indazole-3-carboxylic acid

and

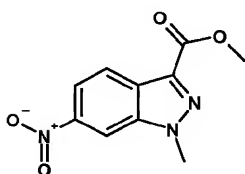


5

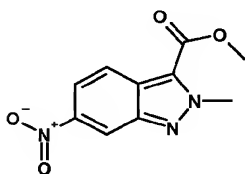
2-methyl-6-nitro-2H-indazole-3-carboxylic acid

670 mg of a mixture of methyl 1-methyl-6-nitro-1H-indazole-3-carboxylate and methyl 2-methyl-6-nitro-2H-indazole-3-carboxylate (Example LV) are dissolved in 20 ml of ethanol, combined with 10 ml of 1 M sodium hydroxide solution and stirred for 2 hours. Then 10 ml of 1 M hydrochloric acid are added, the mixture is diluted with water and the precipitated solid is suction filtered. Then the solid is dissolved in dichloromethane/methanol 90:10. After drying with magnesium sulphate the solvents are eliminated in vacuo and the residue is dried in vacuo. 640 mg of a mixture of 1-methyl-6-nitro-1H-indazole-3-carboxylic acid and 2-methyl-6-nitro-2H-indazole-3-carboxylic acid is obtained, which is further reacted directly in Example XLII (13) or in XLII (14).

20

Example LIVmethyl 1-methyl-6-nitro-1H-indazole-3-carboxylate

and



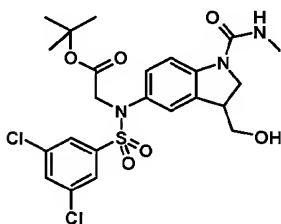
25

methyl 2-methyl-6-nitro-2H-indazole-3-carboxylate

830 mg of 6-nitro-1H-indazole-3-carboxylic acid are dissolved in 16 ml dimethylformamide, combined with 1.66 g potassium carbonate and 823 µl methyl iodide and stirred for 4 hours at 50°C. After cooling to ambient

- 5 temperature the mixture is divided between water and ethyl acetate. The aqueous phase is extracted twice with ethyl acetate and the combined organic phases are washed with saturated sodium chloride solution. After drying with magnesium sulphate the solvents are eliminated in vacuo. The residue is dissolved in hot dimethylformamide and after cooling to ambient temperature
10 the precipitated solid is suction filtered and washed with diethyl ether. 670 mg of a mixture of methyl 1-methyl-6-nitro-1H-indazole-3-carboxylate and methyl 2-methyl-6-nitro-2H-indazole-3-carboxylate is obtained, which is further reacted directly in Example LIII.

15 Example LV

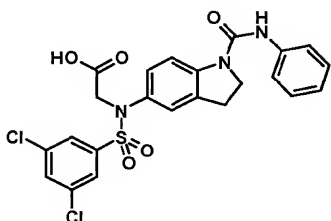


tert. butyl [(3,5-dichloro-phenylsulphonyl)-(3-hydroxymethyl-1-methylcarbamoyl-2,3-dihydro-1H-indol-5-yl)-amino]-acetate

- 20 110 mg methyl 5-[tert-butoxycarbonylmethyl-(3,5-dichloro-phenylsulphonyl)-amino]-1-methylcarbamoyl-2,3-dihydro-1H-indole-3-carboxylate are dissolved in 3 ml of tetrahydrofuran, cooled to 0°C, combined with 4.2 mg lithium borohydride and stirred for 1 hour. Then the mixture is allowed to come up to ambient temperature and stirred overnight. Then it is divided between ethyl
25 acetate and ice water, the pH is adjusted to 4 by the addition of citric acid and the phases are separated. The organic phase is washed with water and saturated sodium chloride solution, dried on magnesium sulphate and freed from the solvents in vacuo. The residue is chromatographed on silica gel (ethyl acetate).
30 Yield: 43 mg (41 % of theory)
Mass spectrum (ESI⁺): m/z = 544 [M+H]⁺

5 Preparation of the end compounds:

Example 1



10

[(3,5-dichloro-phenylsulphonyl)-(1-phenylcarbamoyl-2,3-dihydro-1H-indol-5-yl)-amino]-acetic acid

1.24 g tert. butyl [(3,5-dichloro-phenylsulphonyl)-(1-phenylcarbamoyl-2,3-dihydro-1H-indol-5-yl)-amino]-acetate are dissolved in 10 ml dichloromethane.

15 5 ml of trifluoroacetic acid is added with stirring. The mixture is stirred for 2 hours at ambient temperature and then the solvents are eliminated in vacuo.

The residue is extracted from diisopropylether and cyclohexane.

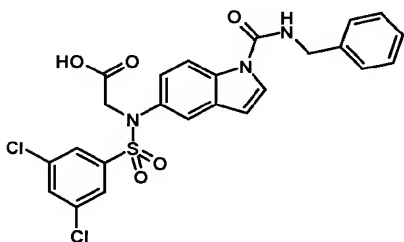
Yield: 1.09 g (97 % of theory)

Mass spectrum (ESI⁺): m/z = 520 [M+H]⁺

20

The following compounds are obtained analogously to Example 1:

(1) [(1-benzylcarbamoyl-1H-indol-5-yl)-(3,5-dichloro-phenylsulphonyl)-amino]-acetic acid

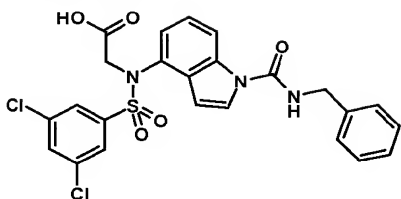


25

Mass spectrum (ESI⁺): m/z = 532 [M+H]⁺

(2) [(1-benzylcarbamoyl-1H-indol-4-yl)-(3,5-dichloro-phenylsulphonyl)-amino]-

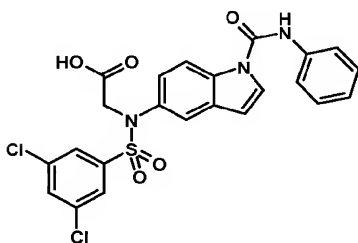
5 acetic acid



Mass spectrum (ESI⁺): m/z = 532 [M+H]⁺

(3) [(3,5-dichloro-phenylsulphonyl)-(1-phenylcarbamoyl-1H-indol-5-yl)-amino]-

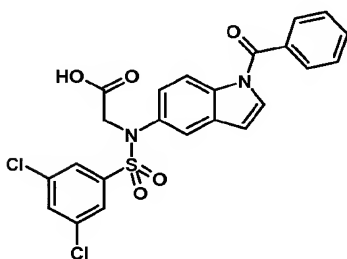
10 acetic acid



Mass spectrum (ESI⁺): m/z = 518 [M+H]⁺

(4) [(1-benzoyl-1H-indol-5-yl)-(3,5-dichloro-phenylsulphonyl)-amino]-acetic

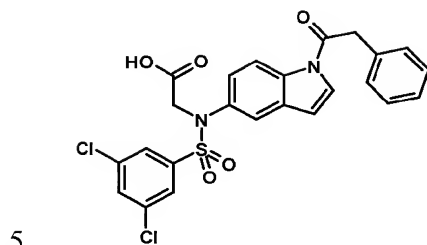
15 acid



Mass spectrum (ESI⁻): m/z = 501 [M-H]⁻

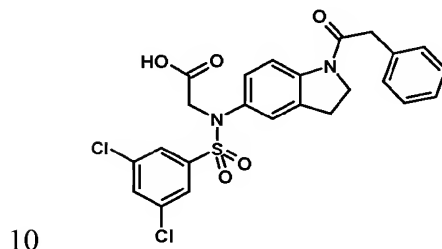
(5) [(3,5-dichloro-phenylsulphonyl)-(1-phenylacetyl-1H-indol-5-yl)-amino]-

20 acetic acid



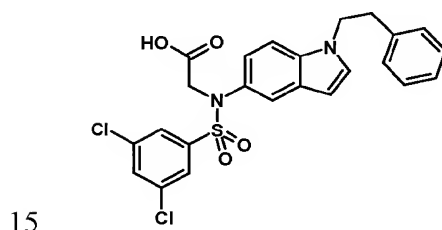
Mass spectrum (ESI⁺): m/z = 517 [M+H]⁺

(6) [(3,5-dichloro-phenylsulphonyl)-(1-phenylacetyl-2,3-dihydro-1H-indol-5-yl)-amino]-acetic acid



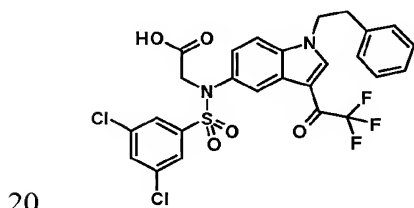
Mass spectrum (ESI⁺): m/z = 519 [M+H]⁺

(7) {(3,5-dichloro-phenylsulphonyl)-[1-(phenylethyl)-1H-indol-5-yl]-amino}-acetic acid



Mass spectrum (ESI⁺): m/z = 503 [M+H]⁺

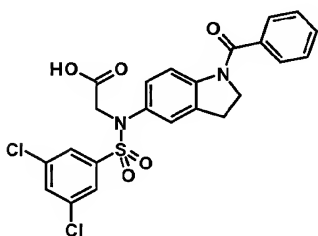
(8) {(3,5-dichloro-phenylsulphonyl)-[1-(phenylethyl)-3-(2,2,2-trifluoro-acetyl)-1H-indol-5-yl]-amino}-acetic acid



- 5 Obtained as a by-product of the cleaving of tert. butyl {(3,5-dichloro-phenylsulphonyl)-[1-(phenylethyl)-1H-indol-5-yl]-amino}-acetate to form {(3,5-dichloro-phenylsulphonyl)-[1-(phenylethyl)-1H-indol-5-yl]-amino}-acetic acid. The products are separated by preparative HPLC.
Mass spectrum (ESI⁻): m/z = 597 [M-H]⁻

10

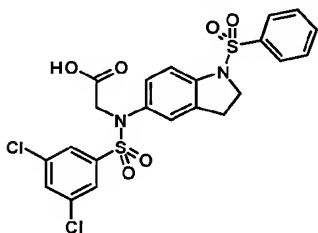
- (9) [(1-benzoyl-2,3-dihydro-1H-indol-5-yl)-(3,5-dichloro-phenylsulphonyl)-amino]-acetic acid



Mass spectrum (ESI⁺): m/z = 505 [M+H]⁺

15

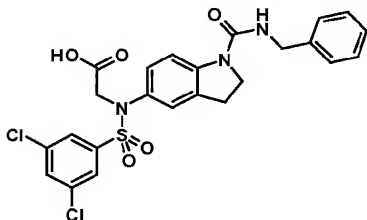
- (10) [(1-phenylsulphonyl-2,3-dihydro-1H-indol-5-yl)-(3,5-dichloro-phenylsulphonyl)-amino]-acetic acid



Mass spectrum (ESI⁻): m/z = 539 [M-H]⁻

20

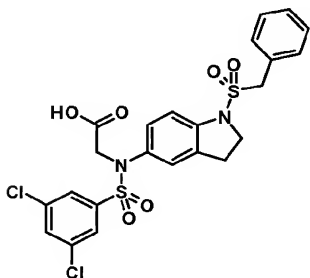
- (11) [(1-benzylcarbamoyl-2,3-dihydro-1H-indol-5-yl)-(3,5-dichloro-phenylsulphonyl)-amino]-acetic acid



Mass spectrum (ESI⁺): m/z = 534 [M+H]⁺

5

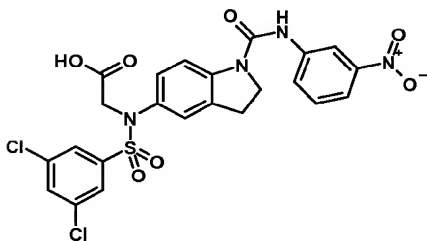
(12) [(3,5-dichloro-phenylsulphonyl)-(1-phenylmethanesulphonyl-2,3-dihydro-1H-indol-5-yl)-amino]-acetic acid



Mass spectrum (ESI⁻): m/z = 553 [M-H]⁻

10

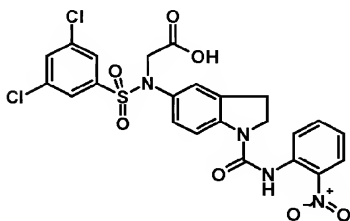
(13) {(3,5-dichloro-phenylsulphonyl)-[1-(3-nitro-phenylcarbamoyl)-2,3-dihydro-1H-indol-5-yl]-amino}-acetic acid



Mass spectrum (ESI⁺): m/z = 565 [M+H]⁺

15

(14) {(3,5-dichloro-phenylsulphonyl)-[1-(2-nitro-phenylcarbamoyl)-2,3-dihydro-1H-indol-5-yl]-amino}-acetic acid

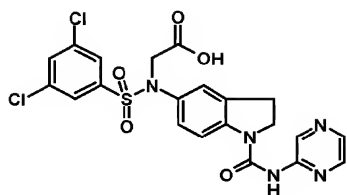


Mass spectrum (ESI⁺): m/z = 565 [M+H]⁺

20

(15) {(3,5-dichloro-phenylsulphonyl)-[1-(pyrazin-2-ylcarbamoyl)-2,3-dihydro-1H-indol-5-yl]-amino}-acetic acid

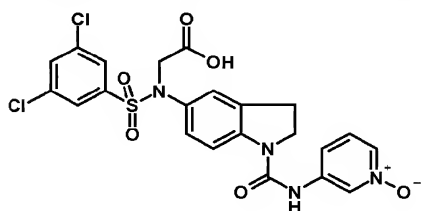
5



Mass spectrum (ESI^-): $m/z = 520$ $[\text{M}-\text{H}]^-$

(16) {(3,5-dichloro-phenylsulphonyl)-[1-(1-oxy-pyridin-3-ylcarbamoyl)-2,3-dihydro-1H-indol-5-yl]-amino}-acetic acid

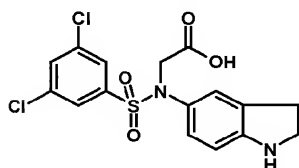
10



Mass spectrum (ESI^+): $m/z = 537$ $[\text{M}+\text{H}]^+$

(17) [(3,5-dichloro-phenylsulphonyl)-(2,3-dihydro-1H-indol-5-yl)-amino]-acetic acid $\cdot \text{CF}_3\text{CO}_2\text{H}$

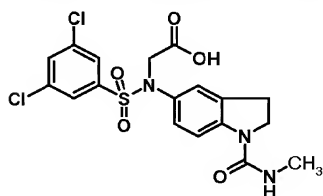
15



Mass spectrum (ESI^+): $m/z = 401$ $[\text{M}+\text{H}]^+$

(18) [(3,5-dichloro-phenylsulphonyl)-(1-methylcarbamoyl-2,3-dihydro-1H-indol-5-yl)-amino]-acetic acid

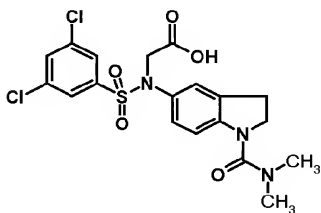
20



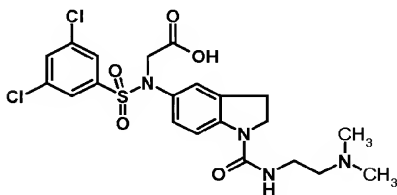
Mass spectrum (ESI^+): $m/z = 458$ $[\text{M}+\text{H}]^+$

(19) [N-(3,5-dichloro-phenyl-sulphonyl)-N-(1-dimethylcarbamoyl-2,3-dihydro-

5 1H-indol-5-yl)-amino]-acetic acid

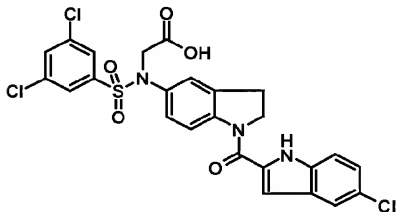


Mass spectrum (ESI⁺): m/z = 472 [M+H]⁺

10 (20) {N-(3,5-dichloro-phenylsulphonyl)-N-[1-(2-dimethylamino-ethylcarbamoyl)-2,3-dihydro-1H-indol-5-yl]-amino}-acetic acid * CF₃CO₂H

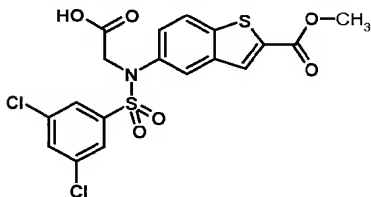
Mass spectrum (ESI⁺): m/z = 515 [M+H]⁺

15 (21) [[1-(5-chloro-1H-indol-2-carbonyl)-2,3-dihydro-1H-indol-5-yl]-(3,5-dichloro-phenylsulphonyl)-amino]-acetic acid



Mass spectrum (ESI⁺): m/z = 578 [M+H]⁺

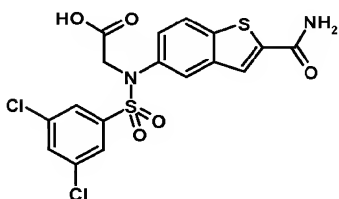
20 (22) methyl 5-[carboxymethyl-(3,5-dichloro-phenylsulphonyl)-amino]-benzo[b]thiophene-2-carboxylate



Mass spectrum (ESI⁻): m/z = 472 [M-H]⁻

5

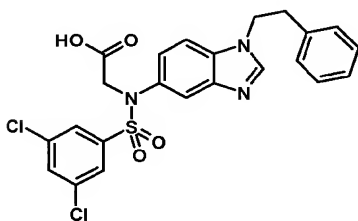
(23) [(2-carbamoyl-benzo[b]thiophene-5-yl)-(3,5-dichloro-phenylsulphonyl)-amino]-acetic acid



Mass spectrum (ESI⁺): m/z = 459 [M+H]⁺

10

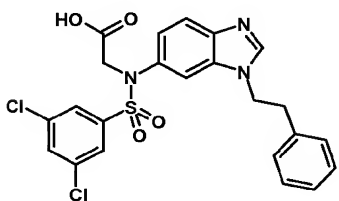
(24) {(3,5-dichloro-phenylsulphonyl)-[1-(phenylethyl)-1H-benzimidazol-5-yl]-amino}-acetic acid * CF₃CO₂H



Mass spectrum (ESI⁺): m/z = 504 [M+H]⁺

15

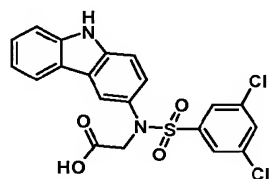
(25) {(3,5-dichloro-phenylsulphonyl)-[3-(phenylethyl)-3H-benzimidazol-5-yl]-amino}-acetic acid * CF₃CO₂H



Mass spectrum (ESI⁺): m/z = 504 [M+H]⁺

20

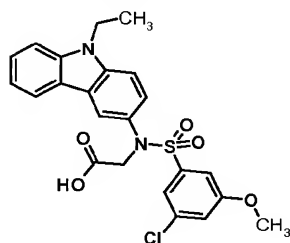
(26) [(9H-carbazol-3-yl)-(3,5-dichloro-phenylsulphonyl)-amino]-acetic acid



The crude product is chromatographed on silica gel.

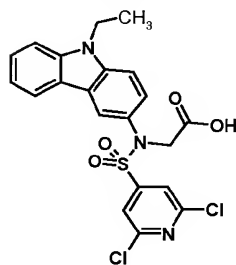
- 5 Mass spectrum (ESI⁺): m/z = 449 [M+H]⁺

(27) [(3-chloro-5-methoxy-phenylsulphonyl)-(9-ethyl-9H-carbazol-3-yl)-amino]-acetic acid



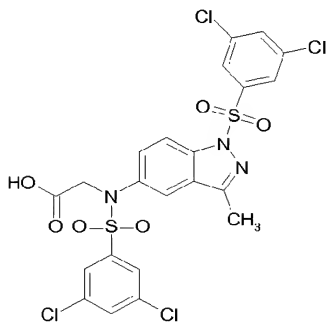
- 10 The crude product is chromatographed on silica gel.
Mass spectrum (ESI⁺): m/z = 473 [M+H]⁺

(28) [(2,6-dichloro-pyridine-4-sulphonyl)-(9-ethyl-9H-carbazol-3-yl)-amino]-acetic acid



- 15 Mass spectrum (ESI⁺): m/z = 478 [M+H]⁺

(29) {(3,5-dichloro-phenylsulphonyl)-[1-(3,5-dichloro-phenylsulphonyl)-3-methyl-1H-indazol-5-yl]-amino}-acetic acid

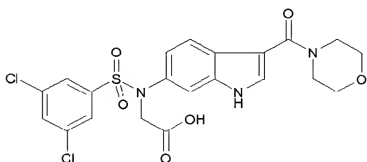


- 20 Mass spectrum (ESI⁻): m/z = 620 [M-H]⁻

R_f value: 0.30 (silica gel: dichloromethane/methanol 95:5)

5

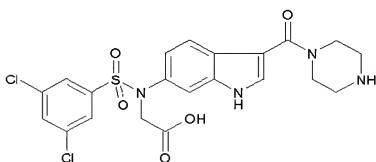
(30) {(3,5-dichloro-phenylsulphonyl)-[3-(morpholine-4-carbonyl)-1H-indol-6-yl]-amino}-acetic acid



Mass spectrum (ESI⁺): m/z = 512 [M+H]⁺

10

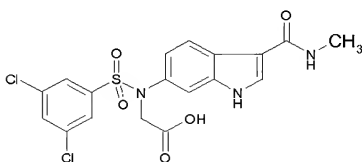
(31) {(3,5-dichloro-phenylsulphonyl)-[3-(piperazine-1-carbonyl)-1H-indol-6-yl]-amino}-acetic acid * CF₃CO₂H



Mass spectrum (ESI⁺): m/z = 511 [M+H]⁺

15

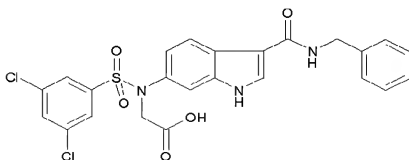
(32) [(3,5-dichloro-phenylsulphonyl)-(3-methylcarbamoyl-1H-indol-6-yl)-amino]-acetic acid



Mass spectrum (ESI⁻): m/z = 454 [M-H]⁻

20

(33) [(3-benzylcarbamoyl-1H-indol-6-yl)-(3,5-dichloro-phenylsulphonyl)-amino]-acetic acid

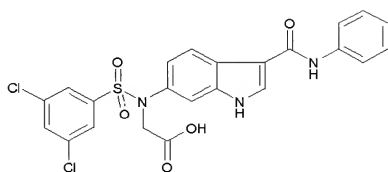


Mass spectrum (ESI⁺): m/z = 532 [M+H]⁺

25

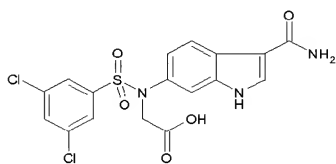
(34) [(3,5-dichloro-phenylsulphonyl)-(3-phenylcarbamoyl-1H-indol-6-yl)-

5 amino]-acetic acid



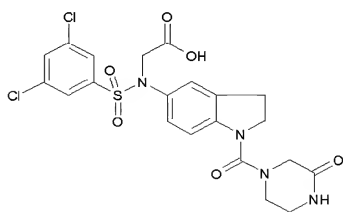
Mass spectrum (ESI⁺): m/z = 518 [M+H]⁺

10 (35) [(3-carbamoyl-1H-indol-6-yl)-(3,5-dichloro-phenylsulphonyl)-amino]-acetic acid



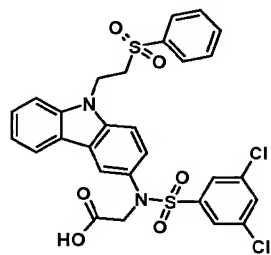
Mass spectrum (ESI⁺): m/z = 442 [M+H]⁺

15 (36) {(3,5-dichloro-phenylsulphonyl)-[1-(3-oxo-piperazine-1-carbonyl)-2,3-dihydro-1H-indol-5-yl]-amino}-acetic acid



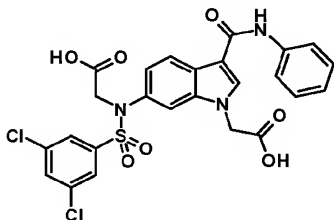
Mass spectrum (ESI⁺): m/z = 527 [M+H]⁺

20 (37) [[9-(2-phenylsulphonyl-ethyl)-9H-carbazol-3-yl]-(3,5-dichloro-phenylsulphonyl)-amino]-acetic acid



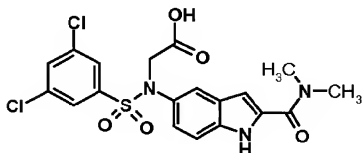
Mass spectrum (ESI⁻): m/z = 615 [M-H]⁻

- 5 (38) {6-[carboxymethyl-(3,5-dichloro-phenylsulphonyl)-amino]-3-phenylcarbamoyl-indol-1-yl}-acetic acid



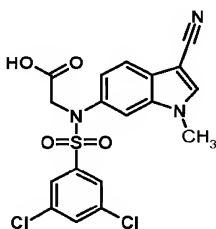
Mass spectrum (ESI⁻): m/z = 574 [M-H]⁻

- 10 (39) [(3,5-dichloro-phenylsulphonyl)-(2-dimethylcarbamoyl-1H-indol-5-yl)-amino]-acetic acid



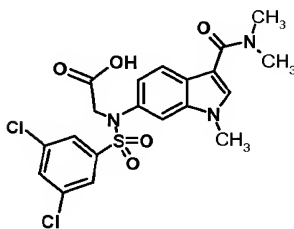
Mass spectrum (ESI⁺): m/z = 470 [M+H]⁺

- 15 (40) [(3-cyano-1-methyl-1H-indol-6-yl)-(3,5-dichloro-phenylsulphonyl)-amino]-acetic acid



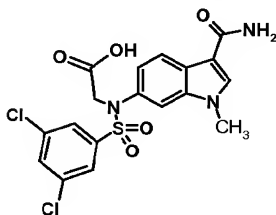
Mass spectrum (ESI⁺): m/z = 438 [M+H]⁺

- 20 (41) [(3,5-dichloro-phenylsulphonyl)-(3-dimethylcarbamoyl-1-methyl-1H-indol-6-yl)-amino]-acetic acid



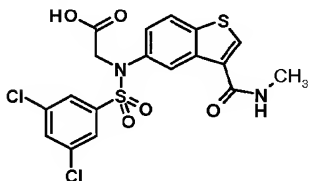
- 5 Mass spectrum (ESI^+): $m/z = 484$ $[\text{M}+\text{H}]^+$

(42) [(3-carbamoyl-1-methyl-1H-indol-6-yl)-(3,5-dichloro-phenylsulphonyl)-amino]-acetic acid



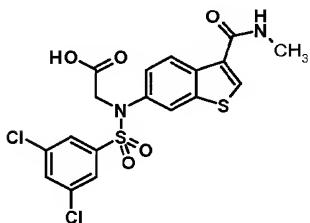
- 10 Mass spectrum (ESI^+): $m/z = 456$ $[\text{M}+\text{H}]^+$

(43) [(3,5-dichloro-phenylsulphonyl)-(3-methylcarbamoyl-benzo[b]thiophene-5-yl)-amino]-acetic acid



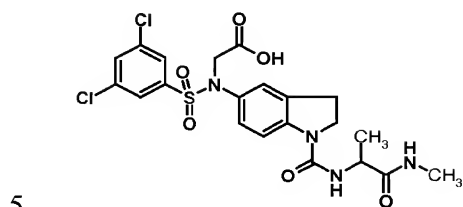
- 15 Mass spectrum (ESI^-): $m/z = 471$ $[\text{M}-\text{H}]^-$

(44) [(3,5-dichloro-phenylsulphonyl)-(3-methylcarbamoyl-benzo[b]thiophene-6-yl)-amino]-acetic acid



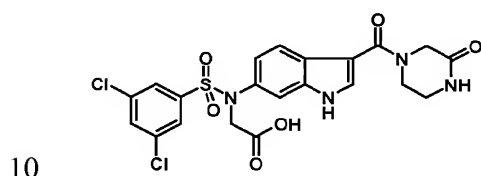
- 20 Mass spectrum (ESI^-): $m/z = 471$ $[\text{M}-\text{H}]^-$

(45) {(3,5-dichloro-phenylsulphonyl)-[1-(1-methylcarbamoyl-ethylcarbamoyl)-2,3-dihydro-1H-indol-5-yl]-amino}-acetic acid



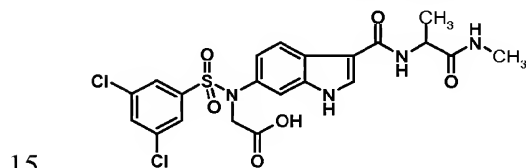
Mass spectrum (ESI⁻): m/z = 527 [M-H]⁻

(46) {(3,5-dichloro-phenylsulphonyl)-[3-(3-oxo-piperazine-1-carbonyl)-1H-indol-6-yl]-amino}-acetic acid



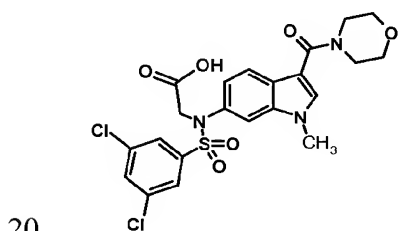
Mass spectrum (ESI⁺): m/z = 525 [M+H]⁺

(47) {(3,5-dichloro-phenylsulphonyl)-[3-(1-methylcarbamoyl-ethylcarbamoyl)-1H-indol-6-yl]-amino}-acetic acid



Mass spectrum (ESI⁺): m/z = 527 [M+H]⁺

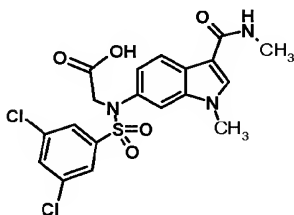
(48) {(3,5-dichloro-phenylsulphonyl)-[1-methyl-3-(morpholine-4-carbonyl)-1H-indol-6-yl]-amino}-acetic acid



Mass spectrum (ESI⁺): m/z = 526 [M+H]⁺

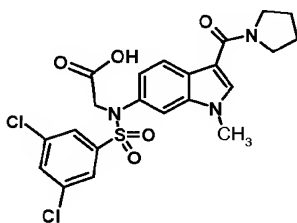
(49) [(3,5-dichloro-phenylsulphonyl)-(1-methyl-3-methylcarbamoyl-1H-indol-6-

5 yl)-amino]-acetic acid



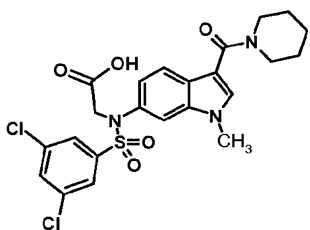
Mass spectrum (ESI⁺): m/z = 470 [M+H]⁺

(50) {(3,5-dichloro-phenylsulphonyl)-[1-methyl-3-(pyrrolidine-1-carbonyl)-1H-
10 indol-6-yl]-amino}-acetic acid



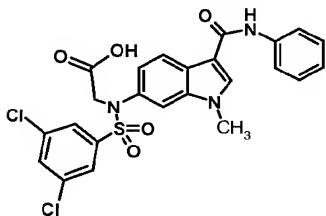
Mass spectrum (ESI⁺): m/z = 510 [M+H]⁺

(51) {(3,5-dichloro-phenylsulphonyl)-[1-methyl-3-(piperidine-1-carbonyl)-1H-
15 indol-6-yl]-amino}-acetic acid



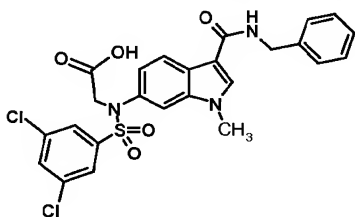
Mass spectrum (ESI⁺): m/z = 524 [M+H]⁺

(52) [(3,5-dichloro-phenylsulphonyl)-(1-methyl-3-phenylcarbamoyl-1H-indol-6-
20 yl)-amino]-acetic acid



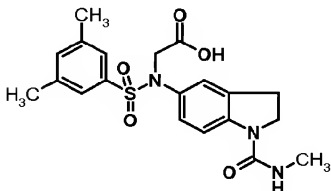
- 5 Mass spectrum (ESI^+): $m/z = 532$ $[\text{M}+\text{H}]^+$

(53) [(3-benzylcarbamoyl-1-methyl-1H-indol-6-yl)-(3,5-dichloro-phenylsulphonyl)-amino]-acetic acid



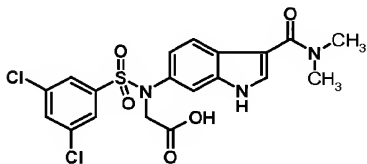
- 10 Mass spectrum (ESI^-): $m/z = 544$ $[\text{M}-\text{H}]^-$

(54) [(3,5-dimethyl-phenylsulphonyl)-(1-methylcarbamoyl-2,3-dihydro-1H-indol-5-yl)-amino]-acetic acid



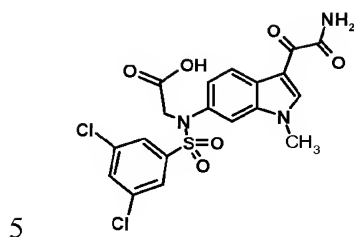
- 15 Mass spectrum (ESI^+): $m/z = 418$ $[\text{M}+\text{H}]^+$

(55) [(3,5-dichloro-phenylsulphonyl)-(3-dimethylcarbamoyl-1H-indol-6-yl)-amino]-acetic acid



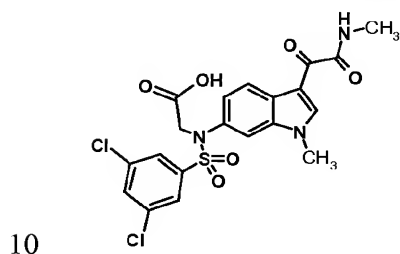
- 20 Mass spectrum (ESI^+): $m/z = 470$ $[\text{M}+\text{H}]^+$

(56) [(3-aminooxalyl-1-methyl-1H-indol-6-yl)-(3,5-dichloro-phenylsulphonyl)-amino]-acetic acid



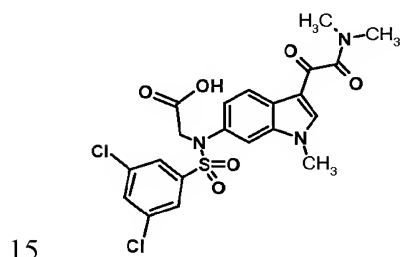
Mass spectrum (ESI⁻): m/z = 482 [M-H]⁻

(57) [(3,5-dichloro-phenylsulphonyl)-(1-methyl-3-methylaminooxalyl-1H-indol-6-yl)-amino]-acetic acid



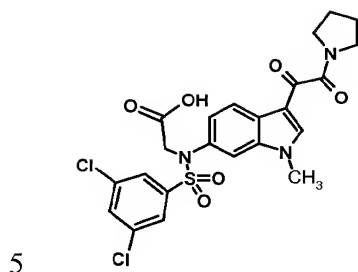
Mass spectrum (ESI⁺): m/z = 498 [M+H]⁺

(58) [(3,5-dichloro-phenylsulphonyl)-(3-dimethylaminooxalyl-1-methyl-1H-indol-6-yl)-amino]-acetic acid



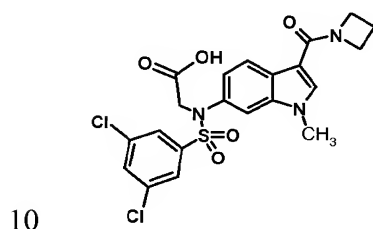
Mass spectrum (ESI⁺): m/z = 512 [M+H]⁺

(59) {(3,5-dichloro-phenylsulphonyl)-[1-methyl-3-(2-oxo-2-pyrrolidin-1-yl-acetyl)-1H-indol-6-yl]-amino}-acetic acid



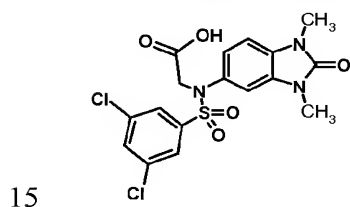
Mass spectrum (ESI⁻): m/z = 536 [M-H]⁻

(60) [[3-(azetidine-1-carbonyl)-1-methyl-1H-indol-6-yl]-(3,5-dichloro-phenylsulphonyl)-amino]-acetic acid



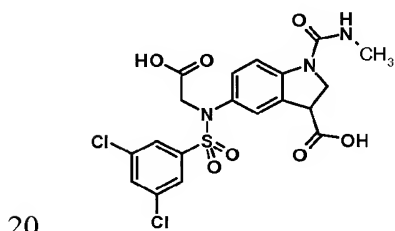
Mass spectrum (ESI⁺): m/z = 496 [M+H]⁺

(61) [(3,5-dichloro-phenylsulphonyl)-(1,3-dimethyl-2-oxo-2,3-dihydro-1H-benzimidazol-5-yl)-amino]-acetic acid



Mass spectrum (ESI⁺): m/z = 444 [M+H]⁺

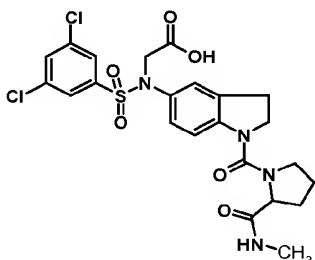
(62) 5-[carboxymethyl-(3,5-dichloro-phenylsulphonyl)-amino]-1-methylcarbamoyl-2,3-dihydro-1H-indole-3-carboxylic acid



Mass spectrum (ESI⁻): m/z = 500 [M-H]⁻

5

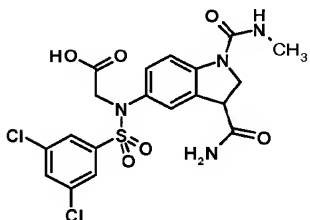
(63) {(3,5-dichloro-phenylsulphonyl)-[1-(2-methylcarbamoyl-pyrrolidine-1-carbonyl)-2,3-dihydro-1H-indol-5-yl]-amino}-acetic acid



Mass spectrum (ESI⁺): m/z = 555 [M+H]⁺

10

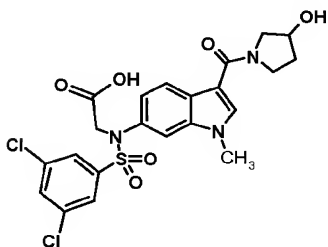
(64) [(3-carbamoyl-1-methylcarbamoyl-2,3-dihydro-1H-indol-5-yl)-(3,5-dichloro-phenylsulphonyl)-amino]-acetic acid



Mass spectrum (ESI⁺): m/z = 501 [M+H]⁺

15

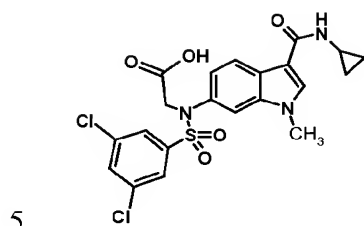
(65) {(3,5-dichloro-phenylsulphonyl)-[3-(3-hydroxy-pyrrolidine-1-carbonyl)-1-methyl-1H-indol-6-yl]-amino}-acetic acid



Mass spectrum (ESI⁺): m/z = 526 [M+H]⁺

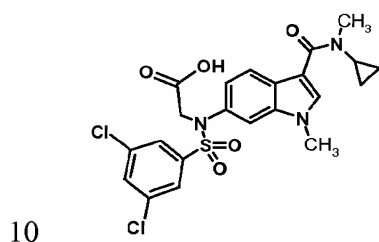
20

(66) [(3-cyclopropylcarbamoyl-1-methyl-1H-indol-6-yl)-(3,5-dichloro-phenylsulphonyl)-amino]-acetic acid



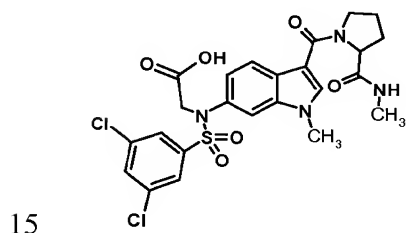
Mass spectrum (ESI⁺): m/z = 496 [M+H]⁺

(67) [[3-(cyclopropyl-methyl-carbamoyl)-1-methyl-1H-indol-6-yl]-(3,5-dichloro-phenylsulphonyl)-amino]-acetic acid



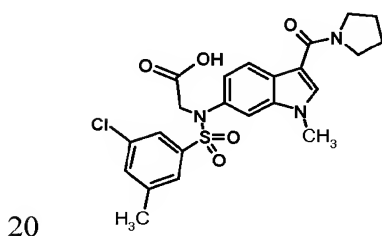
Mass spectrum (ESI⁺): m/z = 510 [M+H]⁺

(68) {(3,5-dichloro-phenylsulphonyl)-[1-methyl-3-(2-methylcarbamoyl-pyrrolidine-1-carbonyl)-1H-indol-6-yl]-amino}-acetic acid



Mass spectrum (ESI⁺): m/z = 567 [M+H]⁺

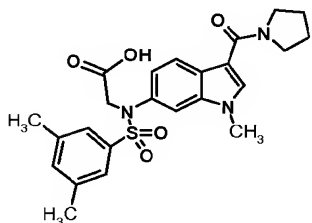
(69) {(3-chloro-5-methyl-phenylsulphonyl)-[1-methyl-3-(pyrrolidine-1-carbonyl)-1H-indol-6-yl]-amino}-acetic acid



Mass spectrum (ESI⁺): m/z = 490 [M+H]⁺

5

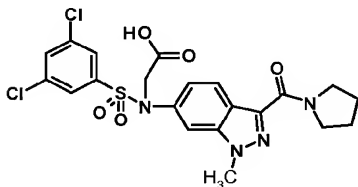
(70) {(3,5-dimethyl-phenylsulphonyl)-[1-methyl-3-(pyrrolidine-1-carbonyl)-1H-indol-6-yl]-amino}-acetic acid



Mass spectrum (ESI⁺): m/z = 470 [M+H]⁺

10

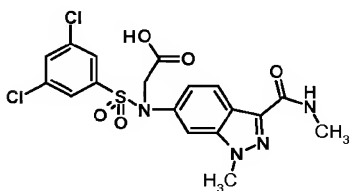
(71) {(3,5-dichloro-phenylsulphonyl)-[1-methyl-3-(pyrrolidine-1-carbonyl)-1H-indazol-6-yl]-amino}-acetic acid



Mass spectrum (ESI⁺): m/z = 511 [M+H]⁺

15

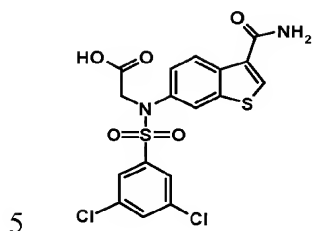
(72) [(3,5-dichloro-phenylsulphonyl)-(1-methyl-3-methylcarbamoyl-1H-indazol-6-yl)-amino]-acetic acid



Mass spectrum (ESI⁺): m/z = 471 [M+H]⁺

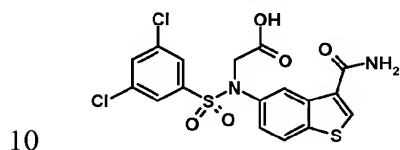
20

(73) [(3-carbamoyl-benzo[b]thiophene-6-yl)-(3,5-dichloro-phenylsulphonyl)-amino]-acetic acid



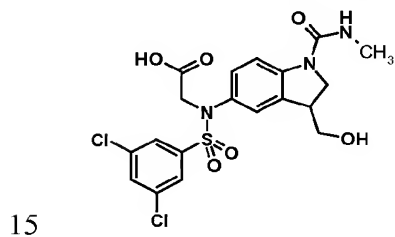
Mass spectrum (ESI⁺): m/z = 476 [M+NH₄]⁺

(74) [(3-carbamoyl-benzo[b]thiophene-5-yl)-(3,5-dichloro-phenylsulphonyl)-amino]-acetic acid



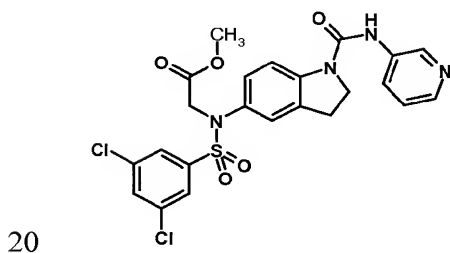
Mass spectrum (ESI⁻): m/z = 457 [M-H]⁻

(75) [(3,5-dichloro-phenylsulphonyl)-(3-hydroxymethyl-1-methylcarbamoyl-2,3-dihydro-1H-indol-5-yl)-amino]-acetic acid



Mass spectrum (ESI⁺): m/z = 488 [M+H]⁺

Example 2



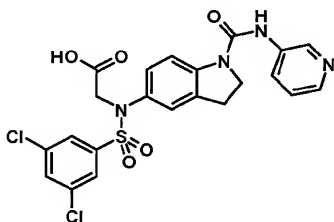
Methyl [(3,5-dichloro-phenylsulphonyl)-[1-(pyridin-3-ylcarbamoyl)-2,3-dihydro-

5 1H-indol-5-yl]-amino}-acetate

610 mg tert-butyl 5-[(3,5-dichloro-phenylsulphonyl)-methoxycarbonylmethyl-amino]-2,3-dihydro-indole-1-carboxylate are dissolved in 8 ml dichloromethane. 4 ml of trifluoroacetic acid are added with stirring. The mixture is stirred for 2 hours at ambient temperature and then the solvents are eliminated in vacuo. The residue is divided between saturated sodium hydrogen carbonate solution and ethyl acetate. The aqueous phase is extracted twice with ethyl acetate. The combined organic phases are dried on sodium sulphate. The solvents are eliminated in vacuo and the residue is taken up in 10 ml dichloromethane. 245 mg potassium carbonate and 150 mg 3-pyridylisocyanate are added and the mixture is stirred overnight at ambient temperature. The solvent is eliminated in vacuo and the residue is divided between water and ethyl acetate. A solid is precipitated which is suction filtered and dried in vacuo.

Yield: 340 mg (54 % of theory)

20 Mass spectrum (ESI⁺): m/z = 535 [M+H]⁺

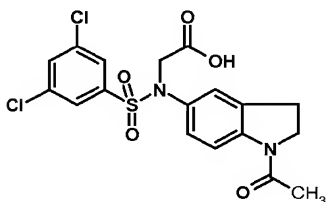
Example 3

25 {(3,5-dichloro-phenylsulphonyl)-[1-(pyridin-3-ylcarbamoyl)-2,3-dihydro-1H-indol-5-yl]-amino}-acetic acid

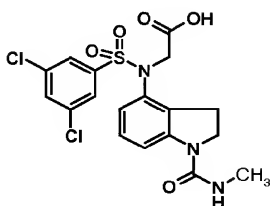
220 mg tert. butyl [(3,5-dichloro-phenylsulphonyl)-(2,3-dihydro-1H-indol-5-yl)-amino]-acetate are dissolved in 10 ml dichloromethane. 166 mg potassium carbonate and 121 mg 3-pyridylisocyanate are added and the mixture is stirred overnight at ambient temperature. The reaction mixture is divided between water and dichloromethane. The aqueous phase is extracted twice with dichloromethane and the combined organic phases are dried on sodium

- 5 sulphate. The solvent is eliminated in vacuo and the residue is taken up in 8 ml dichloromethane. 4 ml trifluoroacetic acid are added and the mixture is stirred for 2 hours at ambient temperature. The solvents are eliminated in vacuo and the residue is extracted from diisopropylether and petroleum ether. The solid is suction filtered and dried in vacuo.
- 10 Mass spectrum (ESI⁺): m/z = 521 [M+H]⁺

Example 4



- 15 [(1-acetyl-2,3-dihydro-1H-indol-5-yl)-(3,5-dichloro-phenylsulphonyl)-amino]-acetic acid
- 40 mg [(3,5-dichloro-phenylsulphonyl)-(2,3-dihydro-1H-indol-5-yl)-amino]-acetic acid are dissolved in 2 ml dichloromethane. 100 µl acetic anhydride are added and the mixture is stirred overnight at ambient temperature. The
- 20 volatile constituents are eliminated in vacuo and the residue is purified by chromatography on silica gel with dichloromethane/methanol (99:1 to 85:15). The product thus obtained is extracted from diethyl ether/diisopropylether. The solid is suction filtered and dried in vacuo.
- Yield: 15 mg (34 % of theory)
- 25 Mass spectrum (ESI⁺): m/z = 443 [M+H]⁺

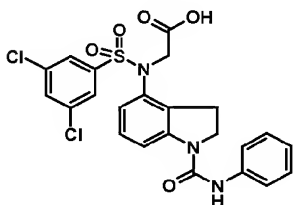
5 Example 5

[(3,5-dichloro-phenylsulphonyl)-(1-methylcarbamoyl-2,3-dihydro-1H-indol-4-yl)-amino]-acetic acid

- 10 300 mg tert. butyl [(3,5-dichloro-phenylsulphonyl)-(1-methylcarbamoyl-2,3-dihydro-1H-indol-4-yl)-amino]-acetate are dissolved in 4 ml of a 4 N solution of HCl in dioxane. The mixture is stirred overnight at RT and the solvents are then eliminated in vacuo. The residue is extracted from dichloromethane.
Yield: 155 mg (58 % of theory)
- 15 Mass spectrum (ESI⁺): m/z = 458 [M+H]⁺

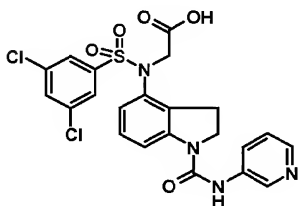
The following compounds are obtained analogously to Example 5:

- (1) [(3,5-dichloro-phenylsulphonyl)-(1-phenylcarbamoyl-2,3-dihydro-1H-indol-4-yl)-amino]-acetic acid
- 20



Mass spectrum (ESI⁺): m/z = 520 [M+H]⁺

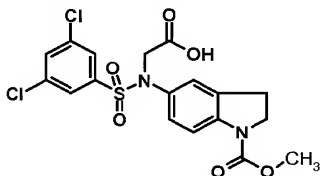
- (2) {(3,5-dichloro-phenylsulphonyl)-[1-(pyridin-3-ylcarbamoyl)-2,3-dihydro-1H-indol-4-yl]-amino}-acetic acid · HCl
- 25



- 5 The crude product is extracted from diethyl ether.

Mass spectrum (ESI⁺): m/z = 521 [M+H]⁺

(3) methyl 5-[carboxymethyl-(3,5-dichloro-phenylsulphonyl)-amino]-2,3-dihydro-indole-1-carboxylate

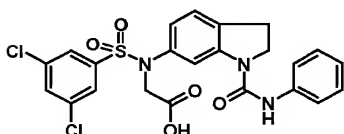


10

After the end of the reaction the dioxane is eliminated in vacuo. The residue is taken up in diethyl ether and the solid is filtered off. The solvent is eliminated in vacuo and the residue is purified by chromatography on silica gel. The product thus obtained is extracted from diisopropylether.

- 15 Mass spectrum (ESI⁺): m/z = 476 [M+H]⁺

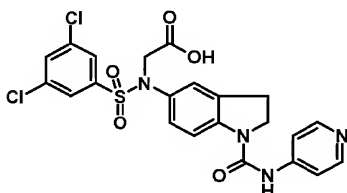
(4) [(3,5-dichloro-phenylsulphonyl)-(1-phenylcarbamoyl-2,3-dihydro-1H-indol-6-yl)-amino]-acetic acid



- 20 The crude product is extracted from diethyl ether.

Mass spectrum (ESI⁺): m/z = 520 [M+H]⁺

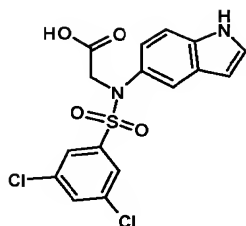
(5) {(3,5-dichloro-phenylsulphonyl)-[1-(pyridin-4-ylcarbamoyl)-2,3-dihydro-1H-indol-5-yl]-amino}-acetic acid · HCl



25

Mass spectrum (ESI⁺): m/z = 521 [M+H]⁺

(6) [(3,5-dichloro-phenylsulphonyl)-(1H-indol-5-yl)-acetic acid



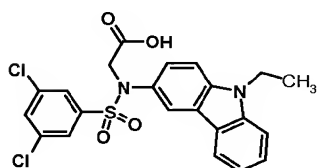
5

The crude product is extracted from diethyl ether.

Mass spectrum (EI): $m/z = 398 [M]^+$

Example 6

10



[(3,5-dichloro-phenylsulphonyl)-(9-ethyl-9H-carbazol-3-yl)-amino]-acetic acid

512 mg methyl [(3,5-dichloro-phenylsulphonyl)-(9-ethyl-9H-carbazol-3-yl)-amino]-acetate are dissolved in 5 ml of tetrahydrofuran. 3 ml 1 N sodium

15 hydroxide solution are added and the mixture is stirred for 3 hours at ambient temperature. It is diluted with ice water and the precipitated solid is suction filtered. The solid is taken up in 15 ml dichloromethane and the organic phase is dried on magnesium sulphate. The solvent is eliminated in vacuo and the residue is chromatographed on silica gel with

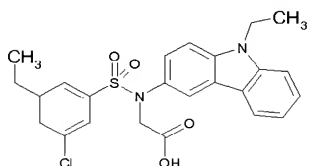
20 dichloromethane/methanol (10:0 to 9:1).

Yield: 24 mg (5 % of theory)

Mass spectrum (ESI⁻): $m/z = 475 [M-H]^-$

Example 7

25



[(3-chloro-5-ethyl-phenylsulphonyl)-(9-ethyl-9H-carbazol-3-yl)-amino]-acetic

5 acid

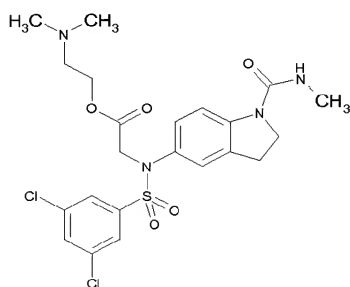
104 mg [(3-chloro-5-ethynyl-phenylsulphonyl)-(9-ethyl-9H-carbazol-3-yl)-amino]-acetic acid are dissolved in 5 ml of ethyl acetate. 30 mg of platinum dioxide are added and the mixture is hydrogenated for 5.5 hours at 3 bar hydrogen pressure. Then the catalyst is removed by suction filtering, the

10 solvent is eliminated in vacuo and the residue is purified by preparative HPLC.
Yield: 38 mg (36 % of theory)

Mass spectrum (ESI⁻): m/z = 469 [M-H]⁻

Example 8

15



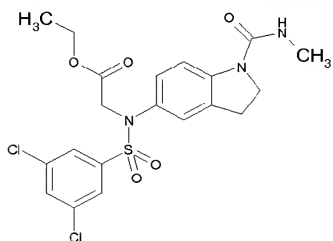
[(3,5-dichloro-phenylsulphonyl)-(1-methylcarbamoyl-2,3-dihydro-1H-indol-5-yl)-amino]-acetic acid-2-dimethylamino-ethylester * HCl

115 mg [(3,5-dichloro-phenylsulphonyl)-(1-methylcarbamoyl-2,3-dihydro-1H-indol-5-yl)-amino]-acetic acid are dissolved in 5 ml of tetrahydrofuran. 90 mg carbonyldiimidazole are added thereto and the mixture is refluxed for 1 hour. After another hour's stirring at ambient temperature 56 µl of 2-dimethylamine-ethanol are added. The mixture is refluxed for 2 hours and stirred for 1 hour at ambient temperature. Then the solvent is eliminated in vacuo and the
25 residue is divided between ethyl acetate and 1 N sodium hydroxide solution. The organic phase is washed once with water and once with saturated sodium chloride solution. After drying with magnesium sulphate the solvent is eliminated in vacuo and the residue is taken up in 4 ml dichloromethane. 100 µl of a 4 N solution of hydrogen chloride in dioxane are added dropwise
30 thereto. The solvent is then eliminated in vacuo and the residue is taken up twice in toluene and the latter is again eliminated in vacuo.

5 Yield: 105 mg (74 % of theory)

Mass spectrum (ESI⁺): m/z = 529 [M+H]⁺

(1) ethyl [(3,5-dichloro-phenylsulphonyl)-(1-methylcarbamoyl-2,3-dihydro-1H-indol-5-yl)-amino]-acetate

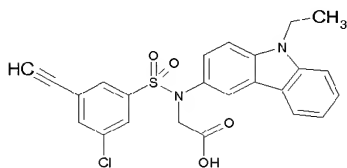


10

After the aqueous working up the crude product is extracted from ethyl acetate, diisopropylether and petroleum ether.

Mass spectrum (ESI⁺): m/z = 486 [M+H]⁺

15 Example 9



[(3-chloro-5-ethynyl-phenylsulphonyl)-(9-ethyl-9H-carbazol-3-yl)-amino]-acetic acid

20 134 mg [(3-chloro-5-trimethylsilylethynyl-phenylsulphonyl)-(9-ethyl-9H-carbazol-3-yl)-amino]-acetic acid are dissolved in 2 ml of methanol, combined with 50 mg potassium carbonate and stirred for 2 hours at ambient temperature. Then the mixture is diluted with dichloromethane and washed with 4 M hydrochloric acid. The organic phase is dried on magnesium sulphate and the solvent is then eliminated in vacuo. The residue is

25 chromatographed on silica gel (dichloromethane/methanol 100:0 to 95:5).

Yield: 108 mg (93 % of theory)

Mass spectrum (ESI⁻): m/z = 465 [M-H]⁻

5

Example 10

Coated tablets containing 75 mg of active substance

1 tablet core contains:

10	active substance	75.0 mg
	calcium phosphate	93.0 mg
	corn starch	35.5 mg
	polyvinylpyrrolidone	10.0 mg
	hydroxypropylmethylcellulose	15.0 mg
15	magnesium stearate	<u>1.5 mg</u>
		230.0 mg

Preparation:

20 The active substance is mixed with calcium phosphate, corn starch, polyvinylpyrrolidone, hydroxypropylmethylcellulose and half the specified amount of magnesium stearate. Blanks 13 mm in diameter are produced in a tablet-making machine and these are then rubbed through a screen with a mesh size of 1.5 mm using a suitable machine and mixed with the rest of the magnesium stearate. This granulate is compressed in a tablet-making machine to form
25 tablets of the desired shape.

Weight of core: 230 mg

die: 9 mm, convex

The tablet cores thus produced are coated with a film consisting essentially of hydroxypropylmethylcellulose. The finished film-coated tablets are polished
30 with beeswax.

Weight of coated tablet: 245 mg.

5 Example 11

Tablets containing 100 mg of active substance

Composition:

1 tablet contains:

10	active substance	100.0 mg
	lactose	80.0 mg
	corn starch	34.0 mg
	polyvinylpyrrolidone	4.0 mg
	magnesium stearate	<u>2.0 mg</u>
15		220.0 mg

Method of Preparation:

20 The active substance, lactose and starch are mixed together and uniformly moistened with an aqueous solution of the polyvinylpyrrolidone. After the moist composition has been screened (2.0 mm mesh size) and dried in a rack-type drier at 50°C it is screened again (1.5 mm mesh size) and the lubricant is added. The finished mixture is compressed to form tablets.

Weight of tablet: 220 mg

25 Diameter: 10 mm, biplanar, facettted on both sides and notched on one side.

5 Example 12

Tablets containing 150 mg of active substance

Composition:

1 tablet contains:

10	active substance	50.0 mg
	powdered lactose	89.0 mg
	corn starch	40.0 mg
	colloidal silica	10.0 mg
	polyvinylpyrrolidone	10.0 mg
15	magnesium stearate	<u>1.0 mg</u>
		300.0 mg

Preparation:

- 20 The active substance mixed with lactose, corn starch and silica is moistened with a 20% aqueous polyvinylpyrrolidone solution and passed through a screen with a mesh size of 1.5 mm. The granules, dried at 45°C, are passed through the same screen again and mixed with the specified amount of magnesium stearate. Tablets are pressed from the mixture.
- 25 Weight of tablet: 300 mg
die: 10 mm, flat

5 Example 13

Hard gelatine capsules containing 150 mg of active substance

1 capsule contains:

	active substance		50.0 mg
10	corn starch (dried	approx.	80.0 mg
	lactose (powdered)	approx.	87.0 mg
	magnesium stearate		<u>3.0 mg</u>
		approx.	420.0 mg

15 Preparation:

The active substance is mixed with the excipients, passed through a screen with a mesh size of 0.75 mm and homogeneously mixed using a suitable apparatus. The finished mixture is packed into size 1 hard gelatine capsules.

Capsule filling: approx. 320 mg

20 Capsule shell: size 1 hard gelatine capsule.

Example 14

Suppositories containing 150 mg of active substance

25 1 suppository contains:

	active substance	150.0 mg
	polyethyleneglycol 1500	550.0 mg
	polyethyleneglycol 6000	460.0 mg
	polyoxyethylene sorbitan monostearate	<u>840.0 mg</u>
30		2,000.0 mg

Preparation:

After the suppository mass has been melted the active substance is homogeneously distributed therein and the melt is poured into chilled moulds.

5

Example 15

Suspension containing 50 mg of active substance

10	100 ml of suspension contain:		
	active substance		1.00 g
	carboxymethylcellulose-Na-salt		0.10 g
	methyl p-hydroxybenzoate		0.05 g
	propyl p-hydroxybenzoate		0.01 g
15	glucose		10.00 g
	glycerol		5.00 g
	70% sorbitol solution		20.00 g
	flavouring		0.30 g
	dist. water	ad	100 ml

20

Preparation:

The distilled water is heated to 70°C. The methyl and propyl p-hydroxybenzoates together with the glycerol and sodium salt of carboxymethylcellulose are dissolved therein with stirring. The solution is cooled to ambient temperature and the active substance is added and homogeneously dispersed therein with stirring. After the sugar, the sorbitol solution and the flavouring have been added and dissolved, the suspension is evacuated with stirring to eliminate air.

30 5 ml of suspension contain 50 mg of active substance.

5 Example 16

Ampoules containing 10 mg active substance

Composition:

	active substance		10.0 mg
10	0.01 N hydrochloric acid q.s.		
	double-distilled water	ad	2.0 ml

Preparation:

The active substance is dissolved in the necessary amount of 0.01 N HCl,
15 made isotonic with common salt, filtered sterile and transferred into 2 ml
ampoules.

Example 17

Ampoules containing 50 mg of active substance

20

Composition:

	active substance		50.0 mg
	0.01 N hydrochloric acid q.s.		
	double-distilled water	ad	10.0 ml

25

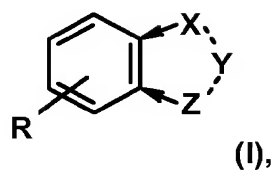
Preparation:

The active substance is dissolved in the necessary amount of 0.01 N HCl,
made isotonic with common salt, filtered sterile and transferred into 10 ml
ampoules.

30

5 Patent Claims

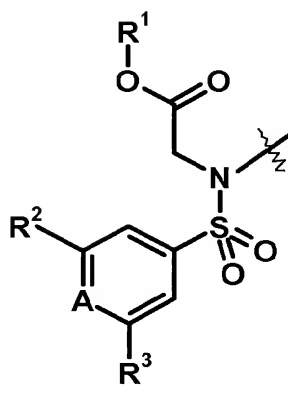
1. Compounds of general formula (I)



10

wherein

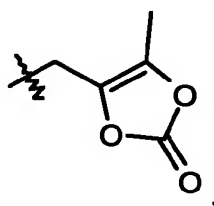
R denotes a group of formula



15

wherein

R¹ denotes H, C₁₋₆-alkyl or a group of formula



20

wherein the C₁₋₆-alkyl group mentioned for R¹ hereinbefore may

5 be substituted by C₁₋₆-alkyl-carbonyloxy, C₁₋₆-alkoxy-carbonyloxy, C₁₋₆-alkoxy, hydroxy, amino, C₁₋₃-alkyl-amino, di-(C₁₋₃-alkyl)-amino, pyrrolidin-1-yl, piperidin-1-yl, morpholin-4-yl, piperazin-1-yl, 4-(C₁₋₃-alkyl)-piperazin-1-yl, aminocarbonyl, C₁₋₃-alkyl-aminocarbonyl, di-(C₁₋₃-alkyl)-aminocarbonyl, pyrrolidin-1-yl-carbonyl, piperidin-1-yl-carbonyl, morpholin-4-yl-carbonyl, 10 piperazin-1-yl-carbonyl, 4-(C₁₋₃-alkyl)-piperazin-1-yl-carbonyl, tetrahydrofuran-3-yl-oxy, C₁₋₃-alkylamino-C₁₋₃-alkyloxy, di-(C₁₋₃-alkyl)-amino-C₁₋₃-alkyloxy, pyrrolidin-1-yl-C₁₋₃-alkyloxy, piperidin-1-yl-C₁₋₃-alkyloxy, morpholin-4-yl-C₁₋₃-alkyloxy, piperazin-1-yl-C₁₋₃-alkyloxy or 4-(C₁₋₃-alkyl)-piperazin-1-yl-C₁₋₃-alkyloxy,

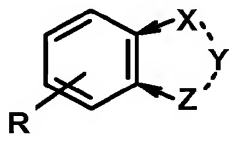
R² and R³ independently of one another denote halogen, C₁₋₃-alkyl, C₂₋₄-alkynyl, C₁₋₃-perfluoroalkyl, C₁₋₃-perfluoroalkoxy, C₁₋₃-alkoxy, cyano, nitro or hydroxy,

20

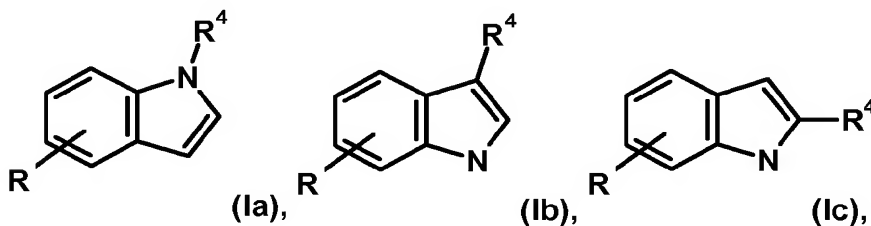
and

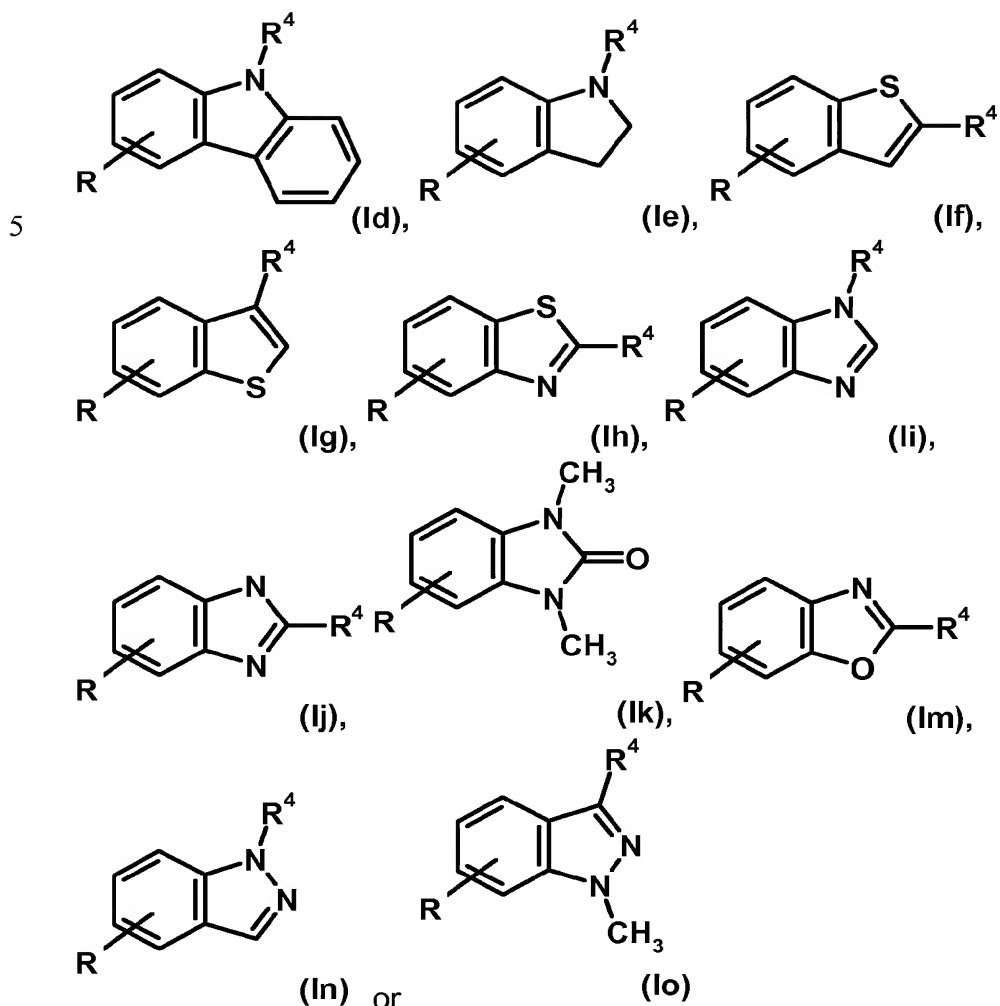
A denotes CH or N,

25 and the heterocyclic group



denotes a group of formula





10 wherein the above-mentioned heterocycles of formulae (Ia), (Ib), (Ic), (Ie), (If), (Ig), (Ii) and (In) may each optionally be substituted at the carbon atoms of the 5 ring by one or two groups selected from among C₁₋₃-alkyl, amino-C₁₋₃-alkyl, hydroxy-C₁₋₃-alkyl, cyano, C₁₋₃-perfluoroalkyl, C₃₋₆-cycloalkyl, C₂₋₄-alkynyl, C₂₋₄-alkenyl, C₁₋₃-alkyl-carbonyl, C₁₋₃-perfluoroalkyl-carbonyl, carboxyl, C₁₋₃-alkyloxy-carbonyl, carboxy-C₁₋₃-alkyl, aminocarbonyl, C₁₋₃-alkyl-aminocarbonyl or di-(C₁₋₃-alkyl)-aminocarbonyl, wherein the groups may be identical or different and each carbon atom may carry only one group, and

20 wherein the above-mentioned heterocyclic group of formula (Ib) may

5 optionally be substituted at the nitrogen atom of the 5 ring by methyl or hydroxycarbonylmethyl, and wherein

R⁴ denotes H, cyano, C₁₋₆-alkyl, phenyl-C₁₋₆-alkyl, phenylsulphonyl-C₁₋₆-alkyl,

10

C₁₋₆-alkyl-carbonyl, carboxyl, C₁₋₆-alkoxy-carbonyl, phenylcarbonyl, phenyl-C₁₋₆-alkyl-carbonyl, 5-chloro-1H-indol-2-yl-carbonyl,

15

aminocarbonyl, C₁₋₆-alkyl-aminocarbonyl, di-(C₁₋₆-alkyl)-aminocarbonyl, C₃₋₆-cycloalkyl-aminocarbonyl, N-(C₃₋₆-cycloalkyl)-N-(C₁₋₆-alkyl)-amino-carbonyl, aryl-amino-carbonyl, N-oxy-pyridylamino-carbonyl,

4- to 7-membered cycloalkyleneimino-carbonyl optionally substituted by hydroxy or C₁₋₃-alkyl-aminocarbonyl,

20

morpholin-4-yl-carbonyl, piperazin-1-yl-carbonyl, 4-(C₁₋₃-alkyl)-piperazin-1-yl-carbonyl, (piperazin-2-on-4-yl)-carbonyl,

25

aminocarbonyl-carbonyl, C₁₋₃-alkylaminocarbonyl-carbonyl, di-(C₁₋₃-alkyl)-aminocarbonyl-carbonyl, pyrrolidin-1-ylcarbonyl-carbonyl, piperidin-1-ylcarbonyl-carbonyl, morpholin-4-ylcarbonyl-carbonyl, piperazin-1-ylcarbonyl-carbonyl, 4-methyl-piperazin-1-ylcarbonyl-carbonyl,

30

C₁₋₃-alkyl-sulphonyl, phenyl-C₁₋₃-alkylsulphonyl or phenylsulphonyl optionally substituted in the phenyl moiety by one or two chlorine atoms,

35

wherein the C₁₋₆-alkyl-aminocarbonyl, di-(C₁₋₆-alkyl)-aminocarbonyl and N-(C₃₋₆-cycloalkyl)-N-(C₁₋₆-alkyl)-amino-carbonyl group mentioned above in the definition of R⁴ may each

5 be substituted in the alkyl moiety by aryl, C₁₋₃-alkyl-amino, di-(C₁₋₃-alkyl)-amino, C₃₋₆-cycloalkyl-amino, N-(C₃₋₆-cycloalkyl)-N-(C₁₋₆-alkyl)-amino, pyrrolidin-1-yl, piperidin-1-yl, morpholin-4-yl, piperazin-1-yl, 4-methyl-piperazin-1-yl or C₁₋₃-alkylaminocarbonyl, and

10

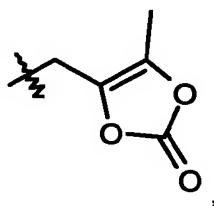
wherein the aryl group mentioned above in the definition of R⁴ is a 6-membered aromatic system that may contain 0 to 3 nitrogen atoms and may be substituted by nitro.

15 and the tautomers, stereoisomers, mixtures thereof and the salts thereof.

2. Compounds of general formula (I) according to claim 1, wherein

20 R denotes a group of the formula given in claim 1, wherein

R¹ denotes H, C₁₋₆-alkyl or a group of formula



25 wherein the C₁₋₆-alkyl group mentioned for R¹ hereinbefore may be substituted by C₁₋₆-alkyl-carbonyloxy, C₁₋₆-alkoxy-carbonyloxy, C₁₋₆-alkoxy, hydroxy, amino, C₁₋₃-alkyl-amino, di-(C₁₋₃-alkyl)-amino, pyrrolidin-1-yl, piperidin-1-yl, morpholin-4-yl, piperazin-1-yl, 4-(C₁₋₃-alkyl)-piperazin-1-yl, aminocarbonyl, C₁₋₃-alkyl-aminocarbonyl, di-(C₁₋₃-alkyl)-aminocarbonyl, pyrrolidin-1-yl-carbonyl, piperidin-1-yl-carbonyl, morpholin-4-yl-carbonyl, piperazin-1-yl-carbonyl or 4-(C₁₋₃-alkyl)-piperazin-1-yl-carbonyl,

30

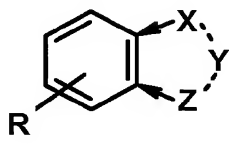
5

R^2 and R^3 independently of one another denote halogen, C_{1-3} -alkyl, C_{2-4} -alkynyl, C_{1-3} -perfluoroalkyl, C_{1-2} -alkoxy or cyano and

A denotes CH or N,

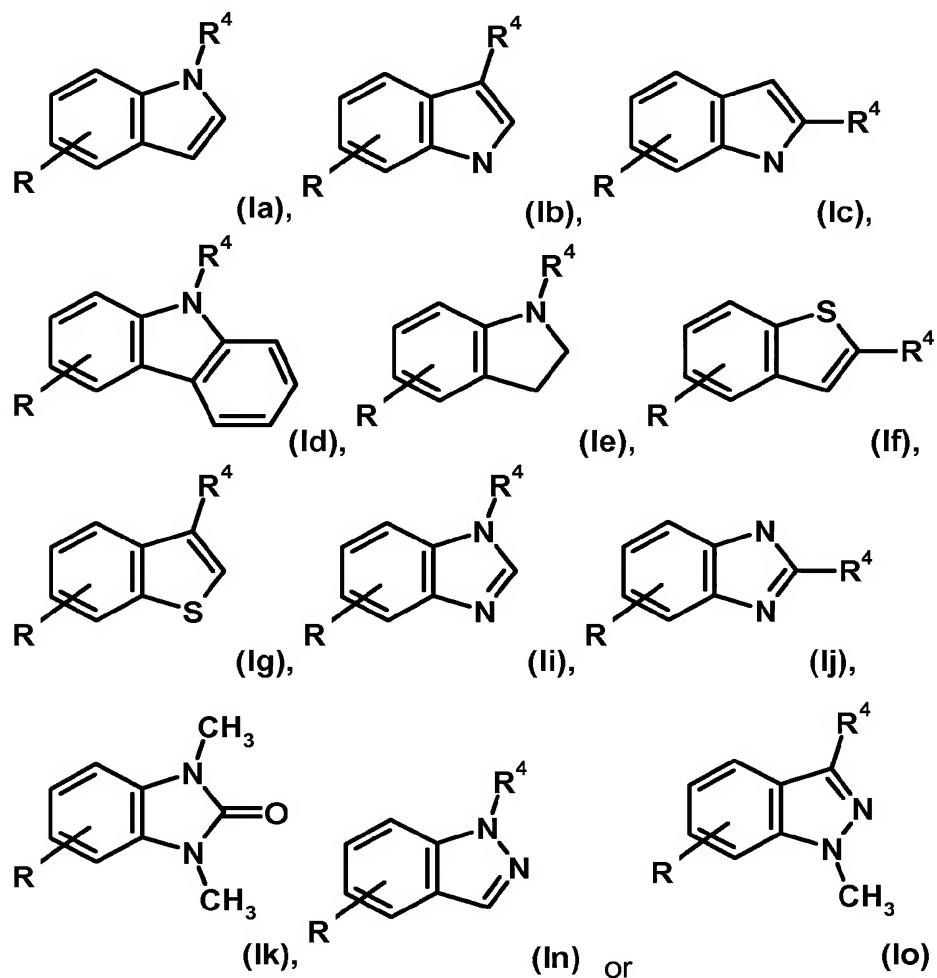
10

and the heterocyclic group



denotes a group of formula

15



5

wherein the above-mentioned heterocycles of formulae (Ia), (Ib), (Ic), (Ie), (If), (Ig), (Ii) and (In) may each optionally be substituted at the carbon atoms of the 5 ring by one or two groups selected from among C₁₋₃-alkyl, amino-C₁₋₃-alkyl, hydroxy-C₁₋₃-alkyl, cyano, C₃₋₆-cycloalkyl, C₁₋₃-alkyl-carbonyl, C₁₋₃-perfluoroalkyl-carbonyl, carboxyl, C₁₋₂-alkyloxy-carbonyl, carboxy-C₁₋₂-alkyl, aminocarbonyl, C₁₋₃-alkyl-aminocarbonyl or di-(C₁₋₃-alkyl)-aminocarbonyl, wherein the groups may be identical or different and each carbon atom may carry only one group, and

10

15

wherein the above-mentioned heterocyclic group of formula (Ib) may optionally be substituted at the nitrogen atom of the 5 ring by methyl or hydroxycarbonylmethyl, and wherein

20

R⁴ denotes H, cyano, C₁₋₄-alkyl, phenyl-C₁₋₄-alkyl, phenylsulphonyl-C₁₋₄-alkyl,

C₁₋₄-alkyl-carbonyl, carboxyl, C₁₋₄-alkoxy-carbonyl, phenylcarbonyl, phenyl-C₁₋₄-alkyl-carbonyl, 5-chloro-1H-indol-2-yl-carbonyl,

25

aminocarbonyl, C₁₋₄-alkyl-aminocarbonyl, di-(C₁₋₄-alkyl)-aminocarbonyl, C₃₋₆-cycloalkyl-aminocarbonyl, N-(C₃₋₆-cycloalkyl)-N-(C₁₋₄-alkyl)-aminocarbonyl, [N,N-di-(C₁₋₄-alkyl)-amino]-C₁₋₃-alkyl-amino-carbonyl, 1-(methylaminocarbonyl)-ethyl-amino-carbonyl, aryl-amino-carbonyl, aryl-C₁₋₃-alkyl-amino-carbonyl, N-oxy-pyridylamino-carbonyl,

30

4- to 7-membered cycloalkyleneimino-carbonyl optionally substituted by hydroxy or methylaminocarbonyl,

35

morpholin-4-yl-carbonyl, piperazin-1-yl-carbonyl, 4-(methyl)-piperazin-1-yl-carbonyl, (piperazin-2-on-4-yl)-carbonyl,

5 aminocarbonyl-carbonyl, C₁₋₂-alkylaminocarbonyl-carbonyl, di-(C₁₋₂-alkyl)-aminocarbonyl-carbonyl, pyrrolidin-1-ylcarbonyl-carbonyl, piperidin-1-ylcarbonyl-carbonyl, morpholin-4-ylcarbonyl-carbonyl, C₁₋₂-alkyl-sulphonyl, phenyl-C₁₋₂-alkyl-sulphonyl or phenylsulphonyl
10 optionally substituted in the phenyl moiety by one or two chlorine atoms,

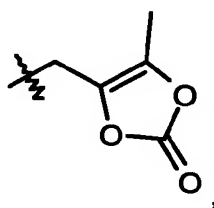
while the aryl group mentioned above in the definition of R⁴ is a 6-membered aromatic system that may contain 0 to 2 nitrogen
15 atoms and may be substituted by nitro,

the tautomers, stereoisomers, mixtures thereof and the salts thereof.

20 3. Compounds of general formula (I) according to claim 2, wherein

R denotes a group of the formula given in claim 1, wherein

R¹ denotes H, C₁₋₄-alkyl or a group of formula



25

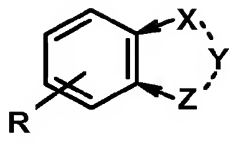
wherein the C₁₋₄-alkyl group mentioned for R¹ hereinbefore may be substituted by C₁₋₄-alkoxy, hydroxy, di-(C₁₋₃-alkyl)-amino, pyrrolidin-1-yl, piperidin-1-yl, morpholin-4-yl, piperazin-1-yl or 4-(methyl)-piperazin-1-yl,
30

R² and R³ independently of one another denote chlorine, bromine, C₁₋₂-

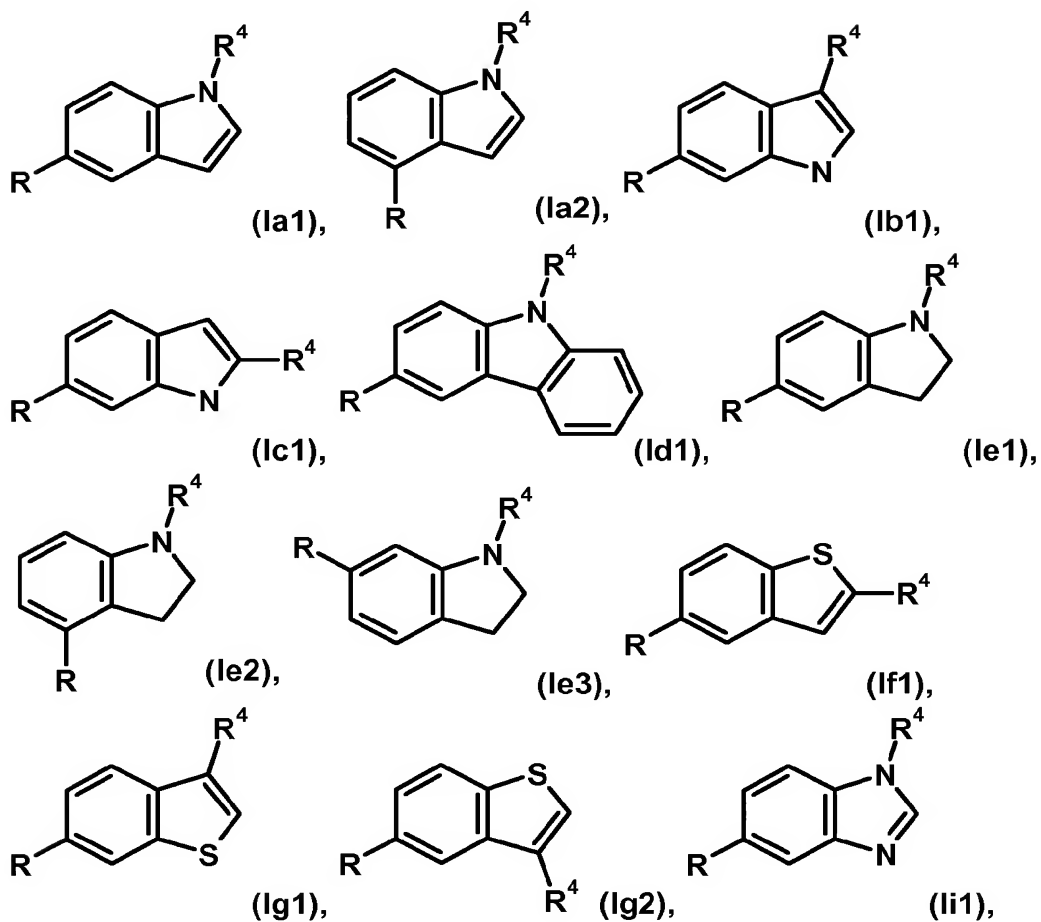
5 alkoxy, C₂₋₃-alkynyl or C₁₋₂-alkyl and

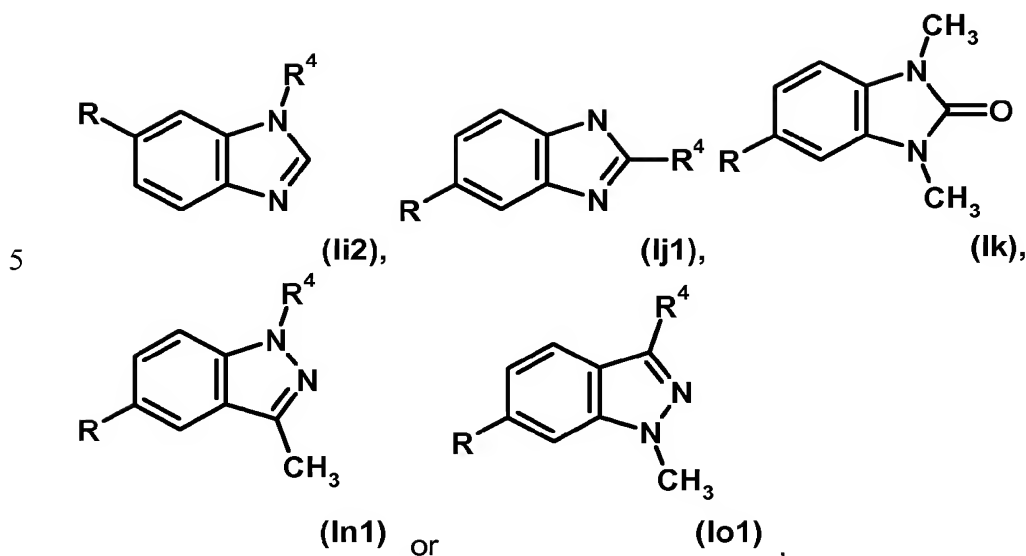
A denotes CH or N,

and the heterocyclic group



denotes a group of formula





10 wherein the above-mentioned heterocycles of formulae (Ia1), (Ia2) and (Ie1) may each optionally be substituted at the carbon atoms of the 5 ring by a group selected from among C₁₋₂-alkyl, methylcarbonyl, trifluoromethylcarbonyl, carboxyl, methoxy-carbonyl, aminocarbonyl, methyl-aminocarbonyl, dimethyl-aminocarbonyl, aminomethyl or hydroxymethyl, and

15 wherein the above-mentioned heterocyclic group of formula (Ib1) may optionally be substituted at the nitrogen atom of the 5 ring by methyl or hydroxycarbonylmethyl, and wherein

20 R⁴ denotes H, cyano, C₁₋₄-alkyl, phenyl-C₁₋₄-alkyl, phenylsulphonyl-C₁₋₄-alkyl,

C₁₋₄-alkyl-carbonyl, carboxyl, C₁₋₄-alkoxy-carbonyl, phenylcarbonyl, phenyl-C₁₋₄-alkyl-carbonyl, 5-chloro-1H-indol-2-yl-carbonyl,

25 aminocarbonyl, C₁₋₄-alkyl-aminocarbonyl, di-(C₁₋₄-alkyl)-aminocarbonyl, C₃₋₆-cycloalkyl-aminocarbonyl, N-(C₃₋₆-cycloalkyl)-N-(C₁₋₄-alkyl)-amino-carbonyl, N,N-di-(C₁₋₃-alkyl)-amino-C₁₋₃-alkyl-amino-carbonyl, 1-

- 5 (methylaminocarbonyl)-ethyl-amino-carbonyl, phenylamino-carbonyl,
(nitrophenyl)-amino-carbonyl, phenyl-C₁₋₂-alkyl-amino-carbonyl,
pyridinylamino-carbonyl, pyrazinylamino-carbonyl, N-oxy-pyridylamino-
carbonyl,
- 10 azetidin-1-yl-carbonyl, pyrrolidin-1-yl-carbonyl, 3-hydroxy-pyrrolidin-1-
yl-carbonyl, 2-(methylaminocarbonyl)-pyrrolidin-1-yl-carbonyl, piperidin-
1-yl-carbonyl, morpholin-4-yl-carbonyl, piperazin-1-yl-carbonyl,
(piperazin-2-on-4-yl)-carbonyl,
- 15 aminocarbonyl-carbonyl, C₁₋₂-alkylaminocarbonyl-carbonyl, di-(C₁₋₂-
alkyl)-aminocarbonyl-carbonyl, pyrrolidin-1-ylcarbonyl-carbonyl,
piperidin-1-ylcarbonyl-carbonyl, morpholin-4-ylcarbonyl-carbonyl,
- benzyl-sulphonyl, phenylsulphonyl or 3,5-dichloro-phenyl-sulphonyl,
- 20 the tautomers, stereoisomers, mixtures thereof and the salts thereof.

4. Compounds of general formula (I) according to claim 3, wherein

R denotes a group of the formula given in claim 1, wherein

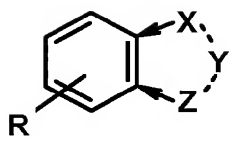
R¹ denotes H or a C₁₋₃-alkyl group optionally substituted by a di-(C₁₋₃-alkyl)-amino group,

R² and R³ independently of one another represent chlorine, ethynyl, methoxy, methyl or ethyl and

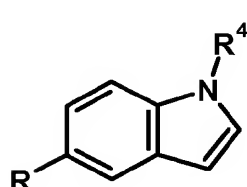
A denotes CH or N,

and the heterocyclic group

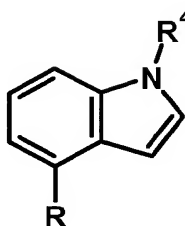
5



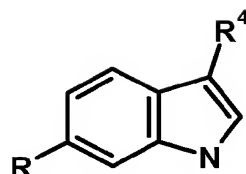
denotes a group of formula



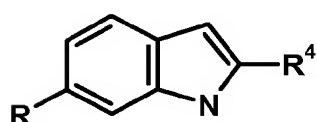
(la1),



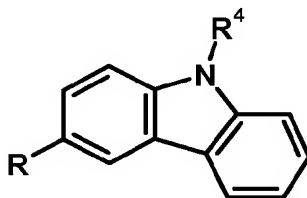
(la2),



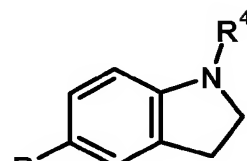
(lb1),



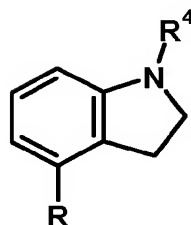
(lc1),



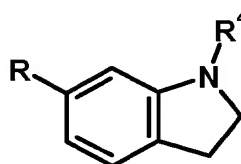
(ld1),



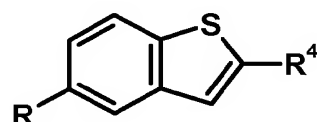
(le1),



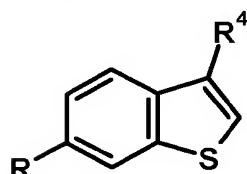
(le2),



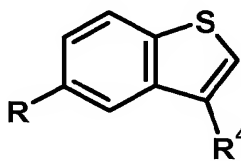
(le3),



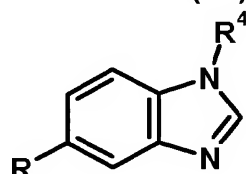
(If1),



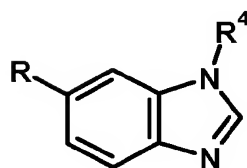
(lg1),



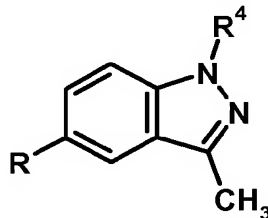
(lg2),



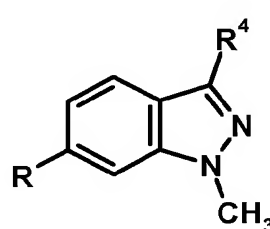
(li1),



(li2),



(ln1) or



(lo1)

wherein the above-mentioned heterocycles of formulae (Ia1) and (Ie1) may each optionally be substituted at the carbon atoms of the 5 ring by

5 a group selected from among C₁₋₂alkyl, trifluoromethylcarbonyl, carboxyl, hydroxycarbonylmethyl, aminocarbonyl or hydroxymethyl, and

10 wherein the above-mentioned heterocyclic group of formula (Ib1) may optionally be substituted at the nitrogen atom of the 5 ring by methyl or hydroxycarbonylmethyl, and wherein

R⁴ denotes H, cyano, C₁₋₃-alkyl, phenyl-C₁₋₂-alkyl, phenylsulphonyl-C₁₋₂-alkyl,

15 C₁₋₃-alkyl-carbonyl, C₁₋₂-alkoxy-carbonyl, phenylcarbonyl, phenyl-C₁₋₂-alkyl-carbonyl, 5-chloro-1H-indol-2-yl-carbonyl,

20 aminocarbonyl, C₁₋₃-alkyl-aminocarbonyl, di-(C₁₋₃-alkyl)-aminocarbonyl, cyclopropyl-aminocarbonyl, N-(cyclopropyl)-N-(C₁₋₂-alkyl)-amino-carbonyl, (N,N-dimethyl-amino)-ethyl-amino-carbonyl, 1-(methylaminocarbonyl)-ethyl-amino-carbonyl, phenylamino-carbonyl, (nitrophenyl)-amino-carbonyl, phenyl-C₁₋₃-alkyl-carbonyl, phenyl-C₁₋₂-alkyl-amino-carbonyl, pyridinylamino-carbonyl, pyrazinylamino-carbonyl, N-oxy-pyridin-3-ylamino-carbonyl,

25 azetidin-1-yl-carbonyl, pyrrolidin-1-yl-carbonyl, 3-hydroxy-pyrrolidin-1-yl-carbonyl, 2-(methylaminocarbonyl)-pyrrolidin-1-yl-carbonyl, piperidin-1-yl-carbonyl, morpholin-4-yl-carbonyl, piperazin-1-yl-carbonyl, 30 (piperazin-2-on-4-yl)-carbonyl,

aminocarbonyl-carbonyl, C₁₋₂-alkylaminocarbonyl-carbonyl, di-(C₁₋₂-alkyl)-aminocarbonyl-carbonyl, pyrrolidin-1-ylcarbonyl-carbonyl,

35 benzyl-sulphonyl or phenyl-sulphonyl,

5 the tautomers, stereoisomers, mixtures thereof and the salts thereof.

5. Compounds of general formula (I) according to claim 4, wherein

10 R denotes a group of the formula given in claim 1, wherein

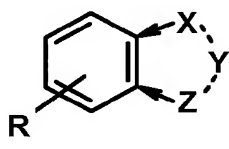
R^1 denotes H, methyl, ethyl or 2-dimethylamino-ethyl,

R^2 and R^3 independently of one another denote chlorine, ethynyl,
15 methoxy, methyl or ethyl and

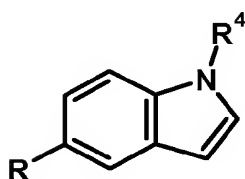
A denotes CH or N,

and the heterocyclic group

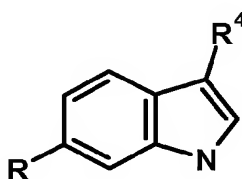
20



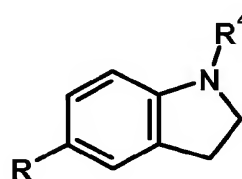
which may be substituted by R^4 as hereinbefore described, denotes a group of formula



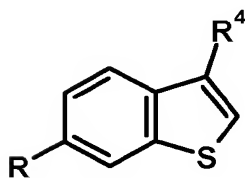
(Ia1),



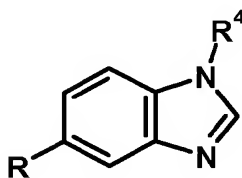
(Ib1),



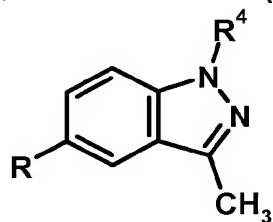
(Ic1),



(Ig1),



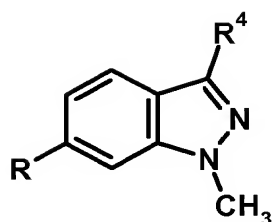
(Ii1),



(In1)

25

or



(Ia1)

wherein the above-mentioned heterocyclic group of formula (Ia1) may optionally be substituted by trifluoromethylcarbonyl at the carbon atom of the 5 ring adjacent to the phenyl ring, and

wherein the above-mentioned heterocyclic group of formula (Ie1) may optionally be substituted by carboxyl, amino-carbonyl or hydroxymethyl at the carbon atom of the 5 ring adjacent to the phenyl ring, and

wherein the above-mentioned heterocyclic group of formula (Ib1) may optionally be substituted by methyl or hydroxycarbonylmethyl at the nitrogen atom of the 5 ring, and wherein

R^4 denotes H, cyano, ethyl, phenyl-ethyl, phenylsulphonyl-ethyl,

methyl-carbonyl, methoxy-carbonyl, phenylcarbonyl, benzylcarbonyl, 5-chloro-1H-indol-2-yl-carbonyl,

aminocarbonyl, methyl-aminocarbonyl, dimethyl-aminocarbonyl, cyclopropyl-aminocarbonyl, N-(cyclopropyl)-N-(methyl)-aminocarbonyl, (N,N-dimethyl-amino)-ethyl-amino-carbonyl, 1-(methylaninocarbonyl)-ethyl-amino-carbonyl, phenylamino-carbonyl, benzylamino-carbonyl, 3-nitro-phenylamino-carbonyl, 2-nitro-phenylamino-carbonyl, pyridin-3-ylamino-carbonyl, pyridin-4-ylamino-carbonyl, pyrazinylamino-carbonyl, N-oxy-pyridin-3-ylamino-carbonyl,

- 5 azetidin-1-yl-carbonyl, pyrrolidin-1-yl-carbonyl, 3-hydroxy-pyrrolidin-1-yl-carbonyl, 2-(methylaminocarbonyl)-pyrrolidin-1-yl-carbonyl, piperidin-1-yl-carbonyl, morpholin-4-yl-carbonyl, piperazin-1-yl-carbonyl, (piperazin-2-on-4-yl)-carbonyl,
- 10 aminocarbonyl-carbonyl, methylaminocarbonyl-carbonyl, dimethylaminocarbonyl-carbonyl, pyrrolidin-1-ylcarbonyl-carbonyl,
- benzyl-sulphonyl or phenyl-sulphonyl,
- 15 the tautomers, stereoisomers, mixtures thereof and the salts thereof.

6. The following compounds according to claim 1:

- ~~(1)~~(1) [(3,5-dichloro-phenylsulphonyl)-(1-phenylcarbamoyl-1H-indol-5-yl)-amino]-acetic acid,
- 20 ~~(2)~~(2) [(3,5-dichloro-phenylsulphonyl)-(1-phenylcarbamoyl-2,3-dihydro-1H-indol-5-yl)-amino]-acetic acid,
- ~~(3)~~(3) {(3,5-dichloro-phenylsulphonyl)-[1-(3-nitro-phenylcarbamoyl)-2,3-dihydro-1H-indol-5-yl]-amino}-acetic acid,
- 25 ~~(4)~~(4) {(3,5-dichloro-phenylsulphonyl)-[1-(pyridin-3-ylcarbamoyl)-2,3-dihydro-1H-indol-5-yl]-amino}-acetic acid,
- ~~(5)~~(5) {(3,5-dichloro-phenylsulphonyl)-[1-(2-nitro-phenylcarbamoyl)-2,3-dihydro-1H-indol-5-yl]-amino}-acetic acid,
- ~~(6)~~(6) [(1-acetyl-2,3-dihydro-1H-indol-5-yl)-(3,5-dichloro-phenylsulphonyl)-amino]-acetic acid,
- 30 ~~(7)~~(7) [(3,5-dichloro-phenylsulphonyl)-(1-methylcarbamoyl-2,3-dihydro-1H-indol-5-yl)-amino]-acetic acid,
- ~~(8)~~(8) {(3,5-dichloro-phenylsulphonyl)-[1-(pyridin-4-ylcarbamoyl)-2,3-dihydro-1H-indol-5-yl]-amino}-acetic acid,
- 35 ~~(9)~~(9) [(2,6-dichloro-pyridine-4-sulphonyl)-(9-ethyl-9H-carbazol-3-yl)-amino]-acetic acid,

- 5 ~~(10)~~(10) {(3,5-dichloro-phenylsulphonyl)-[3-(morpholine-4-carbonyl)-1H-indol-6-yl]-amino}-acetic acid,
 ~~(11)~~(11) [(3,5-dichloro-phenylsulphonyl)-(3-dimethylcarbamoyl-1-methyl-1H-indol-6-yl)-amino]-acetic acid,
 ~~(12)~~(12) [(3,5-dichloro-phenylsulphonyl)-(3-methylcarbamoyl-
10 benzo[b]thiophen-6-yl)-amino]-acetic acid,
 ~~(13)~~(13) {(3,5-dichloro-phenylsulphonyl)-[1-methyl-3-(pyrrolidine-1-carbonyl)-1H-indol-6-yl]-amino}-acetic acid,
 ~~(14)~~(14) [(3,5-dimethyl-phenylsulphonyl)-(1-methylcarbamoyl-2,3-dihydro-1H-indol-5-yl)-amino]-acetic acid,
15 ~~(15)~~(15) [[3-(azetidine-1-carbonyl)-1-methyl-1H-indol-6-yl]-(3,5-dichloro-phenylsulphonyl)-amino]-acetic acid,
 ~~(16)~~(16) {(3,5-dichloro-phenylsulphonyl)-[3-(3-hydroxy-pyrrolidine-1-carbonyl)-1-methyl-1H-indol-6-yl]-amino}-acetic acid,
 ~~(17)~~(17) [[3-(cyclopropyl-methyl-carbamoyl)-1-methyl-1H-indol-6-yl]-(3,5-
20 dichloro-phenylsulphonyl)-amino]-acetic acid,
 ~~(18)~~(18) {(3-chloro-5-methyl-phenylsulphonyl)-[1-methyl-3-(pyrrolidine-1-carbonyl)-1H-indol-6-yl]-amino}-acetic acid,
 ~~(19)~~(19) {(3,5-dimethyl-phenylsulphonyl)-[1-methyl-3-(pyrrolidine-1-carbonyl)-1H-indol-6-yl]-amino}-acetic acid and
25 ~~(20)~~(20) [(3,5-dichloro-phenylsulphonyl)-(3-hydroxymethyl-1-methylcarbamoyl-2,3-dihydro-1H-indol-5-yl)-amino]-acetic acid,

the enantiomers, the mixtures and the salts thereof.

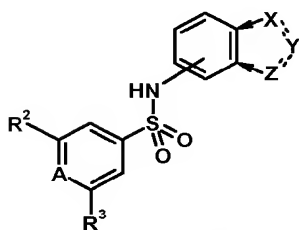
- 30 7. Physiologically acceptable salts of the compounds according to claims 1 to 6 with inorganic or organic acids or bases.
8. Pharmaceutical compositions, containing a compound according to at least one of claims 1 to 6 or a salt according to claim 7 optionally together with
35 one or more inert carriers and/or diluents.

5 9. Use of a compound according to at least one of claims 1 to 6 or a salt according to claim 7 for preparing a pharmaceutical composition that is suitable for the treatment of type I and type II diabetes mellitus.

10 10. Process for preparing a pharmaceutical composition according to claim 8, characterised in that a compound according to at least one of claims 1 to 6 or a salt according to claim 7 is incorporated in one or more inert carriers and/or diluents by a non-chemical method.

15 11. Process for preparing the compounds of general formula I according to claims 1 to 7, characterised in that

a) a compound of general formula (IV)



20 (IV) ,

wherein R², R³, X, Y, Z and A are defined as in claim 1, is alkylated and

25 b) if desired any protective group used to protect reactive groups during the reactions is cleaved afterwards or simultaneously and/or

c) a compound of general formula I thus obtained is resolved into its stereoisomers and/or

30 d) a compound of general formula I thus obtained is converted into the salts thereof, particularly for pharmaceutical use into the physiologically

- 5 acceptable salts thereof with an inorganic or organic acid or base.